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WELCOME TO THE U.S. PATENT TEXT FILE \*\*\*\*\*

=> s (immunoglobulin or immunoglobulin or ig)(w)fusion

6968 IMMUNOGLOBULIN  
281 IMMUNOGLOBULIN  
6055 IG  
39921 FUSION

L1 82 (IMMUNOGLOBULIN OR IMMUNOGLOBULIN OR IG)(W)FUSION  
=> s I1(p)hcg

1358 HCG  
L2 0 L1(P)HCG

=> s fusion protein

39921 FUSION  
60184 PROTEIN  
L3 2942 FUSION PROTEIN  
(FUSION(W)PROTEIN)

=> s chimeric protein

2907 CHIMERIC  
60184 PROTEIN  
L4 308 CHIMERIC PROTEIN  
(CHIMERIC(W)PROTEIN)

=> s I3 or I4

L5 3093 L3 OR L4

=> s I5 and (tnf or cachectin or lymphotoxin)

2241 TNF  
148 CACHECTIN  
350 LYMPHOTOXIN  
L6 274 L5 AND (TNF OR CACHECTIN OR LYMPHOTOXIN)

=> s I5(p)(tnf or cachectin or lymphotoxin)

2241 TNF  
148 CACHECTIN  
350 LYMPHOTOXIN  
L7 47 L5(P)(TNF OR CACHECTIN OR LYMPHOTOXIN)

=> d kwic

US PAT NO: 5,744,304 [IMAGE AVAILABLE] L7: 1  
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SUMMARY:

BSUM(8)

Other . . . have utilized gene therapy methods. For example, using gene transfer vectors in mice (Kolls et al., 1994), researchers constructed a \*\*chimeric\*\* \*\*protein\*\* capable of binding and neutralizing tumor necrosis factor (\*\*TNF\*\*). While the desired effect of producing high levels of constitutively produced \*\*lymphotoxin\*\* was achieved using this system, it was also reported that the animals were rendered highly susceptible to infection by *Listeria*. . .

DETDISC:

DETD(112)

Gene . . . non-replicating adenovirus (6.times.10.sup.12 plaque-forming units) or a DNA-liposome complex (10 mg DNA). The encoded antidote protein may be any of \*\*TNF\*\*-receptor-human immunoglobulin \*\*fusion\*\* \*\*protein\*\*, IL-10, fibrinogen, ACTH, or BPI. To provide multiple recombinant antidote proteins in vivo, more than one kind of vector-antidote protein. . .

=> d kwic 2

US PAT NO: 5,741,774 [IMAGE AVAILABLE] L7: 2  
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SUMMARY:

BSUM(12)

In . . . if the levels of cytokines that contribute to the deleterious effects associated with rheumatoid arthritis could be regulated. For example, \*\*TNF\*\* is believed to have a role in rheumatoid arthritis and administration of a soluble \*\*TNF\*\* receptor fused to an immunoglobulin Fc domain resulted delayed the onset of an experimentally induced arthritis and resulted in a less severe grade of arthritis in mice. This result suggests that such a \*\*fusion\*\* \*\*protein\*\* could be useful for reducing the severity of rheumatoid arthritis.

SUMMARY:

BSUM(13)

Unfortunately, a biological material such as a \*\*TNF\*\* receptor/Fc domain \*\*fusion\*\* \*\*protein\*\* can be expensive to prepare in a form that is sufficiently pure for use as a therapeutic agent. In addition, such a \*\*fusion\*\* \*\*protein\*\* can present "foreign" epitopes that may induce an undesirable immune response in the treated subject. Such an immune response can decrease the effective concentration of the agent in the treated subject by binding to the \*\*fusion\*\* \*\*protein\*\* and can be involved in the formation of immune complexes, which can have deleterious effects in the treated subject. Thus, . . .

=> d kwic 3

US PAT NO: 5,741,667 [IMAGE AVAILABLE] L7: 3  
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DRAWING DESC:

DRWD(10)

(A) The hTNF-R2 was immunoprecipitated from 293 and 293/\*\*TNF\*\*-R2 cells and incubated with lysates from .sup.35 S-labeled CT6 cells that had been preincubated with 50 .mu.l of the indicated GST-hTNF-R2icd \*\*fusion\*\* \*\*protein\*\* beads as competitor. Reactions were analyzed by SDS-PAGE and autoradiography. Arrows indicate bands of 45 to 50-56 kd and 68. . .

DRAWING DESC:

DRWD(13)

FIG. 8. Subcellular localization of \*\*TNF\*\*-R2 associated factors. Cytoplasmic and cell membrane fractions were

prepared from .sup.35 S-labeled CT6 cells as described in the text. These. . . SDS-Page and autoradiography. Arrows indicate bands of 45 to 50-56 kd and 68 kd that coprecipitate specifically with the GST-hTNF-R2icd \*\*fusion\*\* \*\*protein\*\*.

Molecular weight markers are indicated on the right in kd.

DRAWING DESC:

DRWD(15)

Large scale purification of \*\*TNF\*\*<sup>-</sup>R2 associated factors from CT6 cells by GST-hTNF-R2icd \*\*fusion\*\* \*\*protein\*\* affinity chromatography was performed as described in the text. One tenth of the obtained material was analyzed by SDS-PAGE and. . . silver staining. Arrows indicate bands of 45 to 50-56 kd and 68-70 kd that were eluted specifically from the GST-hTNF-R2icd \*\*fusion\*\* \*\*protein\*\* affinity column.

Molecular weight markers are indicated on the right in kd.

DRAWING DESC:

DRWD(29)

FIG. 16. Coprecipitation of GST-TRAF2 \*\*fusion\*\* \*\*protein\*\* in 293 cell extracts. GST and GST-TRAF2 \*\*fusion\*\* \*\*protein\*\* beads were incubated with lysates from 293 and 293TNF-R2 cells as described in the text. Reactions were analyzed by SDS-PAGE and Western blot analysis using anti-human \*\*TNF\*\*<sup>-</sup>R1 monoclonal antibody 986 (0.5 .mu.g/ml) and anti-human \*\*TNF\*\*<sup>-</sup>R2 monoclonal antibody 1036 (0.5 .mu.g/ml). An arrow indicates the 75-80 kd hTNF-R2 band that is coprecipitated specifically with the GST-TRAF2 \*\*fusion\*\* \*\*protein\*\*. Molecular weight markers are indicated on the right in kd.

DETDESC:

DETD(47)

A large-scale purification scheme for purifying factors that associate with the intracellular domain of \*\*TNF\*\*<sup>-</sup>R2 takes advantage of plasmid expression vectors that direct the synthesis of foreign polypeptides in *E. coli* as fusions with the. . . S-transferase (GST), as described by Smith, D. B. and Johnson, K. S., Gene 67 31-40 (1988). The intracellular domain of \*\*TNF\*\*<sup>-</sup>R2 is expressed as a \*\*fusion\*\* \*\*protein\*\* with GST in *E. coli* recombinant host cells, and can be purified from crude bacterial lysates by absorption on glutathione-agarose beads (Sigma). A cell lysate containing the factor(s) to be purified is then applied to a GST-<sup>-</sup>R2 \*\*fusion\*\* \*\*protein\*\* affinity column. Protein(s) bound to the column is/are eluted, precipitated and isolated by SDS-PAGE under reducing conditions, and visualized by. . .

DETDESC:

DETD(213)

Preferably, . . . illustrated in the Examples hereinbelow. Large-scale production and purification of recombinant Glutathione-S-transferase (GST) fusion proteins comprising the cytoplasmic domains of \*\*TNF\*\*<sup>-</sup>R2, CD40 or LMP1 are performed as described in the Examples. For large-scale production of a recombinant TRAF protein, the corresponding. . . (Sigma) for radioactive labeling in vitro. The biochemical screening assay is performed in a robotic automated system in which the GST-<sup>-</sup>R2 or/CD40 or/LMP1 \*\*fusion\*\* \*\*protein\*\* is coated into 96 well microtiterplates and the radioactively labeled TRAF protein added in the presence of various compounds. After. . . unbound TRAF protein and the

captured radioactivity is counted. Inhibitors that prevent the interaction between the TRAF protein and the GST-<sup>-</sup>R2/CD40/LMP1 \*\*fusion\*\* \*\*protein\*\* are identified by decreased captured radioactivity compared with control wells that lack added compounds.

DETDESC:

DETD(215)

Based upon their ability to specifically associate with the intracellular domain of \*\*TNF\*\*<sup>-</sup>R2, the TRAF molecules of the present invention can be used to purify \*\*TNF\*\*<sup>-</sup>R2, which, in turn, is useful in the treatment of various pathological conditions associated with the expression of \*\*TNF\*\*<sup>-</sup>, such as endotoxic (septic) shock and rheumatoid arthritis (RA), either as a soluble \*\*TNF\*\*<sup>-</sup>R2 protein or in the form of an immunoglobulin \*\*fusion\*\* \*\*protein\*\*. The dose regimens effective in the treatment of these and other diseases can be determined by routine experimentation. CD40 and. . .

DETDESC:

DETD(238)

In. . . procedure for factors that associate with the hTNF-R2icd, the intracellular domain of hTNF-R2 was expressed as a glutathione S-transferase (GST) \*\*fusion\*\* \*\*protein\*\* [Smith & Johnson, 1988, supra]. The intracellular domain of hTNF-R2 was amplified from pRK-<sup>-</sup>R2 by PCR with Pfu DNA polymerase as described above using the oligonucleotide primers 5'-GATCGGATCCAAAAGAAGCC CTTGTGCCTGCA-3' (SEQ. ID NO: 31). . . beads were collected by brief centrifugation at 500.times.g and washed extensively with resuspension buffer. An aliquot of the purified GST-hTNF-R2icd \*\*fusion\*\* \*\*protein\*\* was analyzed by SDS-PAGE (FIG. 3). Concentrations of 5-8 mg \*\*fusion\*\* \*\*protein\*\*/ml of swollen beads were obtained routinely.

DETDESC:

DETD(242)

In addition, the GST-hTNF-R2icd(384-424) \*\*fusion\*\* \*\*protein\*\* was able to coprecipitate the bands at 45 to 50-56 kd and 68 kd although to a weaker extent than the other fusion proteins (FIG. 5). The 41 amino acids of the hTNF-R2icd contained in this GST-<sup>-</sup> are comprised within the 78 amino acids region the hTNF-R2icd that has been identified to be required for mediating \*\*TNF\*\*<sup>-</sup> signaling in CT6 cells (see above). This suggests that this short region of the hTNF-R2icd is sufficient to mediate the. . .

DETDESC:

DETD(243)

Competition coprecipitation experiments were performed in which the hTNF-R2 was immunoprecipitated from unlabeled 293<sup>-</sup>R2 cells and then incubated with labeled CT6 cell lysate that had been precleared with 50 .mu.l of GST-hTNF-R2icd \*\*fusion\*\* \*\*protein\*\* beads. Preincubation of the CT6 extracts with GST beads alone or GST-hTNF-R2icd(-37) and GST-hTNF-R2icd(-59) \*\*fusion\*\* \*\*protein\*\* beads had no effect on the pattern of proteins coprecipitating with the immunoprecipitated hTNF-R2 (FIG. 6). However, if the cell lysate had been precleared with GST-hTNF-R2icd or GST-hTNF-R2icd(-16) \*\*fusion\*\* \*\*protein\*\* beads, these proteins did not coprecipitate with the

immunoprecipitated hTNF-R2 (FIG. 6), indicating that they had been depleted from the labeled CT6 cell extract by the GST-hTNF-R2<sub>icd</sub> fusion proteins. This result demonstrates that the wild type GST-hTNF-R2<sub>icd</sub> \*\*fusion\*\* \*\*protein\*\* associates with the same intracellular factors as the immunoprecipitated hTNF-R2. Consequently, this GST-**fusion** **protein** material can be used for large scale purification of factors that are associated with the intracellular domain of the hTNF-R2. . . . coprecipitating proteins very similar in size to the pattern observed with murine CT6 lysates (FIG. 7). This suggests that the **TNF**-R2 associated factors are closely related between the mouse and human species.

DETDESC:

DETD(270)

An expression vector encoding a GST-TRAF2 **fusion** **protein** was constructed. The TRAF2 coding region was amplified from pPC86TRAF2 by PCR with Pfu DNA polymerase as described above using. . . . fragment was blunt-ended using E. coli DNA polymerase I, digested with BamHI and cloned into BamHI/SmaI-digested pGEX-2TK vector. The GST-TRAF2 **fusion** **protein** was expressed in the presence of 1 mM ZnCl<sub>2</sub> and purified as described above. GST and GST-TRAF2 **fusion** **protein** beads were incubated with lysates from 293 and 293/**TNF**-R2 cells, and analyzed by SDS-PAGE and Western blot analysis [Sambrook et al., "Molecular Cloning: A Laboratory Manual. Cold Spring Harbor. . . . the secondary sheep anti-mouse horseradish peroxidase conjugate (Amersham) at a dilution of 1:6000. As shown in FIG. 16, the GST-TRAF2 **fusion** **protein** coprecipitates the hTNF-R2 in 293 cell extracts, thus confirming the results obtained from two hybrid analysis.

DETDESC:

DETD(272)

Cotransformation of pPC86TRAF1 into HF7c cells with the GAL4 DNA-binding **TNF**-R2 fusion constructs encoding the wild type human and murine intracellular domains indicated that the direct interaction between TRAF1 and the intracellular domain of **TNF**-R2 is weak (Table 2). However, cotransformation of pPC97TRAF1 and pPC86TRAF2 or pPC97TRAF2 and pPC86TRAF1 revealed that TRAF1 and TRAF2 interact. . . . each other (Table 2) suggesting that a heterodimeric complex of TRAF1 and TRAF2 is associated with the intracellular domain of **TNF**-R2. Subsequently yeast vectors were constructed in which TRAF2 is expressed directly, i.e. not as a GAL4 **fusion** **protein**. pPC97TRAF2 was digested with HindIII and SalI to release a 0.5 kb DNA fragment encoding the GAL4 DNA-binding domain, end-filled. . . . cells (Table 3). This result confirms that a heterodimeric complex of TRAF1 and TRAF2 interacts with the intracellular domain of **TNF**-R2. In this protein complex mainly TRAF2 contacts the receptor directly potentially through interaction of its RING finger domain with the C-terminal region of the intracellular domain comprising amino acids 304-345 of the human **TNF**-R2 as suggested from mutational analysis and coprecipitation experiments (see above). TRAF1 and TRAF2 can also form homodimeric complexes as shown. . . .

DETDESC:

DETD(279)

TABLE 3

# Interaction between TRAF1, TRAF2 and the Intracellular Domain of **TNF**-R2

(continued)

Transformant

Activation-domain	Growth on trp-
DNA-binding domain hybrid	
hybrid	Direct expression
	leu.sup.- his.sup.- medium

GAL4(DB) GAL4(TA)-TRAF1. . . plasmids (see text) encodin the indicated GAL4 DNAbinding domain (DB) fusion proteins, the GAL4 transcriptional activation domain (TA) TRAF1 **fusion** **protein**, and TRAF2 or TRAF2 fused to the simian virus 40 large tumor antigen nuclear localization signal (NLS). The final. . . .

DETDESC:

DETD(282)

To . . . within the TRAF2 protein that are required for homodimerization, heterodimerization with TRAF1 and for interaction with the cytoplasmic domain of **TNF**-R2 GAL4-TRAF2 **fusion** **protein** vectors were constructed which express mutant TRAF2 proteins. A 1.9 kb DNA fragment which encodes amino acids 87-501 of TRAF2. . . . table 4 indicate that the RING finger domain of TRAF2 is not required for interaction with the cytoplasmic domain of **TNF**-R2 since the mutant TRAF2 protein in which the RING finger domain (amino acids 1-86) was removed was still able to associate with the cytoplasmic domain of **TNF**-R2. Also, this mutant TRAF2 protein could still associate with both TRAF1 and wild-type TRAF2. The same results were obtained for. . . . mediate homo- and heterodimerization of TRAF1 and TRAF2 as well as for interaction of TRAF2 with the cytoplasmic domain of **TNF**-R2.  
=> d 4-14

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- 5,723,437, Mar. 3, 1998, CD6 ligand; Barton F. Haynes, et al., 514/2; 435/69.1; 530/350, 413 [IMAGE AVAILABLE]
- 5,721,121, Feb. 24, 1998, Mammalian cell culture process for producing a tumor necrosis factor receptor immunoglobulin chimeric protein; Tina Etcheverry, et al., 435/69.7, 325, 328, 358, 361; 530/387.3, 395 [IMAGE AVAILABLE]
- 5,716,805, Feb. 10, 1998, Methods of preparing soluble, oligomeric proteins; Subhashini Srinivasan, et al., 435/69.1, 7.2, 69.7, 70.1, 71.1, 172.3, 252.3, 320.1, 325; 530/350; 536/23.1, 23.5 [IMAGE AVAILABLE]
- 5,712,381, Jan. 27, 1998, MADD, a TNF receptor death domain ligand protein; Lih-Ling Lin, et al., 536/23.5; 435/69.1, 70.1, 320.1, 325; 530/300, 350 [IMAGE AVAILABLE]
- 5,712,155, Jan. 27, 1998, DNA encoding tumor necrosis factor-alpha and -beta receptors; Craig A. Smith, et al., 435/320.1; 424/85.1; 435/69.3, 69.5; 530/351, 388.23, 389.2; 536/23.1; 935/12 [IMAGE AVAILABLE]
- 5,708,142, Jan. 13, 1998, Tumor necrosis factor receptor-associated factors; David V. Goeddel, et al., 530/350;

435/69.1, 252.3, 320.1; 536/23.5 [IMAGE AVAILABLE]

11. 5,707,616, Jan. 13, 1998, Method for treating or preventing gastrointestinal disease with epithelium-derived T-cell factor; Kenneth H. Grabstein, et al., 424/85.2; 435/69.52, 252.3, 320.1, 325; 514/2, 8, 12, 885; 530/351 [IMAGE AVAILABLE]

12. 5,705,364, Jan. 6, 1998, Mammalian cell culture process; Tina Etcheverry, et al., 435/70.3, 375, 383, 395 [IMAGE AVAILABLE]

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=> d 15-24

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20. 5,650,150, Jul. 22, 1997, Recombinant antibody cytokine fusion proteins; Stephen D. Gillies, 424/134.1, 85.1, 133.1; 435/69.7 [IMAGE AVAILABLE]

21. 5,643,570, Jul. 1, 1997, BPI-immunoglobulin fusion proteins; Georgia Theofan, et al., 424/134.1; 435/69.1, 172.3, 252.3, 320.1; 530/387.3; 536/23.4 [IMAGE AVAILABLE]

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24. 5,629,285, May 13, 1997, Inhibitors of TNF-.alpha. secretion; Roy A. Black, et al., 514/2, 7, 119, 507, 563; 530/331 [IMAGE AVAILABLE]

=> d 25-34

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=> d 35-44

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36. 5,506,340, Apr. 9, 1996, Tumor necrosis factor inhibitors; George A. Heavner, 530/324, 325, 326, 327, 328, 329, 330 [IMAGE AVAILABLE]

37. 5,486,595, Jan. 23, 1996, Tumor necrosis factor inhibitors; George A. Heavner, 530/324, 325, 326, 327, 328, 329, 330 [IMAGE AVAILABLE]

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factor- $\alpha$ . and - $\beta$ . receptors; Craig A. Smith, et al., 435/365; 424/85.1; 435/69.4, 172.3; 530/351, 388.23; 536/23.51 [IMAGE AVAILABLE]  
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=> d kwic 41

US PAT NO: 5,434,131 [IMAGE AVAILABLE] L7:  
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DETDESC:

DETD(37)

In one embodiment, the CTLA4lg \*\*fusion\*\* \*\*protein\*\* or CTLA4lg/CD28lg hybrid proteins, may be introduced in a suitable pharmaceutical carrier in vivo, i.e. administered-into a human subject for treatment of pathological conditions such as immune system diseases or cancer. Introduction of the \*\*fusion\*\* \*\*protein\*\* in vivo is expected to result in interference with T cell interactions with other cells, such as B cells, as. . . cell interactions may result in decreased T cell activity, for example, decreased T cell proliferation. In addition, administration of the \*\*fusion\*\* \*\*protein\*\* in vivo is expected to result in regulation of in vivo levels of cytokines, including, but not limited to, interleukins,. . . IL-4, IL-6, IL-8, growth factors including tumor growth factor ("TGF"), colony stimulating factor ("CSF"), interferons ("IFNs"), and tumor necrosis factor ("\*\*TNF\*\*") to promote desired effects in a subject. For example, when the \*\*fusion\*\* \*\*protein\*\* is introduced in vivo, it may block production of cytokines, which contribute to malignant growth, for example of tumor cells. The \*\*fusion\*\* \*\*protein\*\* may also block proliferation of viruses dependent on T cell activation, such as the virus that causes AIDS, HTLV1.  
=> d kwic 42

US PAT NO: 5,395,760 [IMAGE AVAILABLE] L7:  
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DETDESC:

DETD(71)

Recombinant human \*\*TNF\*\*.alpha., in the form of a \*\*fusion\*\* \*\*protein\*\* containing a hydrophilic octapeptide at the N-terminus, was expressed in yeast as a secreted protein and purified by affinity chromatography (Hopp et al., Bio/Technology 6:1204, 1988). Purified recombinant human \*\*TNF\*\*.beta. was purchased from R & D Systems (Minneapolis, Minn.). Both proteins were radiolabeled using the commercially available solid phase agent,. . . 20 .mu.l (2 mCi) Na .sup.125 I. This solution was then transferred to a second glass tube containing 5 .mu.g \*\*TNF\*\*.alpha. (or \*\*TNF\*\*.beta.) in 45 .mu.l PBS for 20 minutes at 4.degree. C. The reaction mixture was fractionated by gel filtration on a. . . serum albumin (BSA), 0.2% (w/v) sodium azide and 20 mM Hepes pH 7.4 (binding medium). The final pool of .sup.125 I-**TNF** was diluted to a working stock solution of 1.times.10.sup.-7 M in binding medium and stored for up to one month at 4.degree. C. without detectable loss of receptor binding activity. The specific activity is routinely 1.times.10.sup.6 cpm/mmol **TNF**.

=> d ab 42

US PAT NO: 5,395,760 [IMAGE AVAILABLE] L7:  
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ABSTRACT:

Tumor necrosis factor receptor proteins, DNAs and expression vectors encoding TNF receptors, and processes for producing TNF receptors as products of recombinant cell culture, are disclosed.

=> d ab kwic 40

US PAT NO: 5,447,851 [IMAGE AVAILABLE] L7:  
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ABSTRACT:

The invention relates generally to DNA sequences encoding chimeric polypeptides comprising extracellular portions of cytokine receptor polypeptides attached to a sequence encoding portions of IgG polypeptides. The invention relates generally, as well, to DNA sequences encoding chimeric polypeptides comprising extracellular portions of cytokine receptor polypeptides attached through oligomers encoding specifically cleavable peptide linkers to a sequence encoding portions of IgG heavy chain polypeptides. More specifically, the invention relates to a construction in which a cDNA sequence encoding the extracellular domain of the human 55 kD TNF receptor is attached through an oligomer encoding a thrombin-sensitive peptide linker to a sequence encoding the F.sub.c portion and hinge region of a mouse IgG1 heavy chain. The invention relates as well to uses of the chimeric polypeptide, including: use as a reagent for the antagonism and assay of TNF and lymphotoxin from diverse species; use as a means of determining the mechanism by which TNF, or analogs thereof, interacts with the TNF receptor; use as an antitumor reagent, particularly against placental tumors; and, use as a reagent capable of controlling birth.

SUMMARY:

BSUM(28)

In order to overcome at least some of the limitations of the prior art, the present invention discloses a \*\*chimeric\*\* \*\*protein\*\* in which the extracellular domain of a cytokine receptor, which normally engages the cytokine molecule, is covalently linked to an IgG molecule. In particular, and by way of example, a \*\*TNF\*\* receptor extracellular polypeptide is coupled to the CH.sub.2 through CH.sub.3 regions of a mouse IgG1 heavy chain. Interposed between the. . . protease or other peptide cleaving reagent. In a particular embodiment, a hexapeptide sensitive to cleavage by thrombin is used. The \*\*chimeric\*\* \*\*protein\*\* is expressed and secreted by CHO cells. In another embodiment, the insect cell lines SF9 and SF21 may be used. . . hooked up to the chimeric polypeptide. Whichever vector/host system is utilized, the resulting recombinant chimera is highly active as a \*\*TNF\*\* inhibitor, is readily purified by affinity chromatography using an anti-mouse IgG or Protein A column, and is quantitatively cleaved by. . .

=> xxxxxxxxxxxxxxxx

'XXXXXXXXXXXXXXXX' IS NOT A RECOGNIZED COMMAND

=> d ab kwic 40

US PAT NO: 5,447,851 [IMAGE AVAILABLE] L7:

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ABSTRACT:

The invention relates generally to DNA sequences encoding chimeric polypeptides comprising extracellular portions of cytokine receptor polypeptides attached to a sequence encoding portions of IgG polypeptides. The invention relates generally, as well, to DNA sequences encoding chimeric polypeptides comprising extracellular portions of cytokine receptor polypeptides attached through oligomers encoding specifically cleavable peptide linkers to a sequence encoding portions of IgG heavy chain polypeptides. More specifically, the invention relates to a construction in which a cDNA sequence encoding the extracellular domain of the human 55 kD TNF receptor is attached through an oligomer encoding a thrombin-sensitive peptide linker to a sequence encoding the F.sub.c portion and hinge region of a mouse IgG1 heavy chain. The invention relates as well to uses of the chimeric polypeptide, including: use as a reagent for the antagonism and assay of TNF and lymphotoxin from diverse species; use as a means of determining the mechanism by which TNF, or analogs thereof, interacts with the TNF receptor; use as an antitumor reagent, particularly against placental tumors; and, use as a reagent capable of controlling birth.

SUMMARY:

BSUM(28)

In order to overcome at least some of the limitations of the prior art, the present invention discloses a "chimeric" "protein" in which the extracellular domain of a cytokine receptor, which normally engages the cytokine molecule, is covalently linked to an IgG molecule. In particular, and by way of example, a "TNF" receptor extracellular polypeptide is coupled to the CH.sub.2 through CH.sub.3 regions of a mouse IgG1 heavy chain. Interposed between the . . . protease or other peptide cleaving reagent. In a particular embodiment, a hexapeptide sensitive to cleavage by thrombin is used. The "chimeric" "protein" is expressed and secreted by CHO cells. In another embodiment, the insect cell lines SF9 and SF21 may be used. . . hooked up to the chimeric polypeptide. Whichever vector/host system is utilized, the resulting recombinant chimera is highly active as a "TNF" inhibitor, is readily purified by affinity chromatography using an anti-mouse IgG or Protein A column, and is quantitatively cleaved by. . .

=> d ab kwic 37

US PAT NO: 5,486,595 [IMAGE AVAILABLE] L7:  
37 of 47

ABSTRACT:

Peptides which consist of 4-25 amino acids and which bind to tumor necrosis factor-alpha, prevent tumor necrosis factor-alpha from binding to its receptors and inhibit tumor necrosis factor-alpha activity are disclosed. Methods of inhibiting tumor necrosis factor-alpha activity and of treating individuals suffering from tumor necrosis factor-alpha-mediated diseases and disorders are disclosed.

DETDESC:

DETD(19)

In order to determine whether a peptide inhibits "TNF".alpha., one or more of several assays may be performed. Included among these are assays which measure the ability a "TNF".alpha. inhibitor candidate, i.e. a test compound, to inhibit "TNF".alpha. from binding to a "fusion" "protein" that is composed of a "TNF" receptor or

a

"TNF".alpha.-binding portion thereof, fused to an immunoglobulin molecule or a portion thereof. In other assays, the ability a test compound to inhibit "TNF".alpha. from binding to an isolated "TNF" receptor is measured. Other assays include those which the ability of a "TNF".alpha. inhibitor candidate, i.e. a test compound, to inhibit "TNF".alpha. activity when "TNF".alpha. is contacted with cells that react to the presence of "TNF".alpha.. For example, "TNF".alpha. is cytotoxic to some cells, such as WEHI cells, and assays can be used to measure the ability a test compound, to inhibit "TNF".alpha. cytotoxicity.

DETDESC:

DETD(117)

In order to screen compounds for their ability to block "TNF".alpha. binding to the "TNF" p55 receptor, an assay has been designed using "TNF".alpha. and a p55/IgG "fusion" "protein" in place of monovalent, non-fusion p55 "TNF" receptor protein. This assay was designed to identify peptides which bind to human "TNF".alpha. and thereby prevent the capture of the "TNF".alpha. by a microtiter plate coated with p55-Ig "fusion" "protein". A constant concentration of human "TNF".alpha. is preincubated with the test peptide and then incubated on the p55-Ig coated microtiter wells. Bound "TNF".alpha. is detected using a specific antisera and an alkaline phosphatase-conjugated probe. An active peptide will reduce the amount of human "TNF".alpha. bound to the well relative to control wells in which "TNF".alpha. but no peptide was added.

DETDESC:

DETD(118)

A 96-well, U-bottom polyvinylchloride microtiter plate was coated with 50 .mu.l/well of p55-Ig "fusion" "protein" at 5 .mu.g/ml in 0.01M sodium phosphate, 0.15M sodium chloride (PBS) by incubation overnight at 4.degree. C. or 2 hours at 37.degree. C. The "fusion" "protein", which consists of a p55 "TNF" receptor protein portion and an IgG portion, can be produced as disclosed in U.S. application Ser. No. 08/010,406 filed Jan. . .

=> d ab kwic 37

US PAT NO: 5,486,595 [IMAGE AVAILABLE] L7:  
37 of 47

ABSTRACT:

Peptides which consist of 4-25 amino acids and which bind to tumor necrosis factor-alpha, prevent tumor necrosis factor-alpha from binding to its receptors and inhibit tumor necrosis factor-alpha activity are disclosed. Methods of inhibiting tumor necrosis factor-alpha activity and of treating individuals suffering from tumor necrosis factor-alpha-mediated diseases and disorders are disclosed.

DETDESC:

DETD(19)

In order to determine whether a peptide inhibits "TNF".alpha., one or more of several assays may be performed. Included among these are assays which measure the ability a "TNF".alpha. inhibitor candidate, i.e. a test compound, to inhibit "TNF".alpha. from binding to a "fusion" "protein" that is composed of a "TNF" receptor or

a  
\*\*TNF\*\*.alpha.-binding portion thereof, fused to an immunoglobulin molecule or a portion thereof. In other assays, the ability a test compound to inhibit \*\*TNF\*\*.alpha. from binding to an isolated \*\*TNF\*\* receptor is measured. Other assays include those which the ability of a \*\*TNF\*\*.alpha. inhibitor candidate, i.e. a test compound, to inhibit \*\*TNF\*\*.alpha. activity when \*\*TNF\*\*.alpha. is contacted with cells that react to the presence of \*\*TNF\*\*.alpha.. For example, \*\*TNF\*\*.alpha. is cytotoxic to some cells, such as WEHI cells, and assays can be used to measure the ability a test compound, to inhibit \*\*TNF\*\*.alpha. cytotoxicity.

DETDESC:

DETD(117)

In order to screen compounds for their ability to block \*\*TNF\*\*.alpha. binding to the \*\*TNF\*\* p55 receptor, an assay has been designed using \*\*TNF\*\*.alpha. and a p55/IgG \*\*fusion\*\* \*\*protein\*\* in place of monovalent, non-fusion p55 \*\*TNF\*\* receptor protein. This assay was designed to identify peptides which bind to human \*\*TNF\*\*.alpha. and thereby prevent the capture of the \*\*TNF\*\*.alpha. by a microtiter plate coated with p55-Ig \*\*fusion\*\* \*\*protein\*\*. A constant concentration of human \*\*TNF\*\*.alpha. is preincubated with the test peptide and then incubated on the p55-Ig coated microtiter wells. Bound \*\*TNF\*\*.alpha. is detected using a specific antisera and an alkaline phosphatase-conjugated probe. An active peptide will reduce the amount of human \*\*TNF\*\*.alpha. bound to the well relative to control wells in which \*\*TNF\*\*.alpha. but no peptide was added.

DETDESC:

DETD(118)

A 96-well, U-bottom polyvinylchloride microtiter plate was coated with 50 .mu.l/well of p55-Ig \*\*fusion\*\* \*\*protein\*\* at 5 .mu.g/ml in 0.01M sodium phosphate, 0.15M sodium chloride (PBS) by incubation overnight at 4.degree. C. or 2 hours at 37.degree. C. The \*\*fusion\*\* \*\*protein\*\*, which consists of a p55 \*\*TNF\*\* receptor protein portion and an IgG portion, can be produced as disclosed in U.S. application Ser. No. 08/010,406 filed Jan.. . .

=> d ab kwic 27

US PAT NO: 5,605,690 [IMAGE AVAILABLE] L7:  
27 of 47

ABSTRACT:

A method for treating TNF-dependent inflammatory diseases in a mammal by administering a TNF antagonist, such as soluble TNFR.

DETDESC:

DETD(24)

A . . . a single chimeric antibody molecule having TNFR displayed bivalently. Such polyvalent forms of TNFR may have enhanced binding affinity for \*\*TNF\*\* ligand. One specific example of a TNFR/Fc \*\*fusion\*\* \*\*protein\*\* is disclosed in SEQ ID NO:3 and SEQ ID NO:4. Additional details relating to the construction of such chimeric antibody. . .

=> d ab kwic 22

US PAT NO: 5,641,751 [IMAGE AVAILABLE] L7:  
22 of 47

ABSTRACT:

Peptides which consist of 4-25 amino acids and which bind to tumor necrosis factor-alpha, prevent tumor necrosis factor-alpha from binding to its receptors and inhibit tumor necrosis factor-alpha activity are disclosed. Methods of inhibiting tumor necrosis factor-alpha activity and of treating individuals suffering from tumor necrosis factor-alpha-mediated diseases and disorders are disclosed.  
SUMMARY:

BSUM(44)

In order to determine whether a peptide inhibits \*\*TNF\*\*.alpha., one or more of several assays may be performed. Included among these are assays which measure the ability a \*\*TNF\*\*.alpha. inhibitor candidate, i.e. a test compound, to inhibit \*\*TNF\*\*.alpha. from binding to a \*\*fusion\*\* \*\*protein\*\* that is composed of a \*\*TNF\*\* receptor or a  
a  
\*\*TNF\*\*.alpha.-binding portion thereof, fused to an immunoglobulin molecule or a portion thereof. In other assays, the ability a test compound to inhibit \*\*TNF\*\*.alpha. from binding to an isolated \*\*TNF\*\* receptor is measured. Other assays include those which the ability of a \*\*TNF\*\*.alpha. inhibitor candidate, i.e. a test compound, to inhibit \*\*TNF\*\*.alpha. activity when \*\*TNF\*\*.alpha. is contacted with cells that react to the presence of \*\*TNF\*\*.alpha.. For example, \*\*TNF\*\*.alpha. is cytotoxic to some cells, such as WEHI cells, and assays can be used to measure the ability a test compound, to inhibit \*\*TNF\*\*.alpha. cytotoxicity.

DETDESC:

DETD(3)

In order to screen compounds for their ability to block \*\*TNF\*\*.alpha. binding to the \*\*TNF\*\* p55 receptor, an assay has been designed using \*\*TNF\*\*.alpha. and a p55/IgG \*\*fusion\*\* \*\*protein\*\* in place of monovalent, non-fusion p55 \*\*TNF\*\* receptor protein. This assay was designed to identify peptides which bind to human \*\*TNF\*\*.alpha. and thereby prevent the capture of the \*\*TNF\*\*.alpha. by a microtiter plate coated with p55-Ig \*\*fusion\*\* \*\*protein\*\*. A constant concentration of human \*\*TNF\*\*.alpha. is preincubated with the test peptide and then incubated on the p55-Ig coated microtiter wells. Bound \*\*TNF\*\*.alpha. is detected using a specific antisera and an alkaline phosphatase-conjugated probe. An active peptide will reduce the amount of human \*\*TNF\*\*.alpha. bound to the well relative to control wells in which \*\*TNF\*\*.alpha. but no peptide was added.

DETDESC:

DETD(4)

A 96-well, U-bottom polyvinylchloride microtiter plate was coated with 50 .mu.l/well of p55-Ig \*\*fusion\*\* \*\*protein\*\* at 5 .mu.g/ml in 0.01M sodium phosphate, 0.15M sodium chloride (PBS) by incubation overnight at 4.degree. C. or 2 hours at 37.degree. C. The \*\*fusion\*\* \*\*protein\*\*, which consists of a p55 \*\*TNF\*\* receptor protein portion and an IgG portion, can be produced as disclosed in U.S. application Ser. No. 08/010,406 filed Jan.. . .

=> d ab kwic 20

US PAT NO: 5,650,150 [IMAGE AVAILABLE] L7:  
20 of 47

ABSTRACT:

Immunoconjugates for the selective delivery of a cytokine to a target cell are disclosed. The fusion proteins are comprised of an immunoglobulin heavy chain having a specificity for the target cell, such as a cancer or virus-infected cell, and a cytokine, such as lymphotoxin, tumor necrosis factor alpha, interleukin-2, or granulocyte-macrophage colony stimulating factor, joined via its amino terminal amino acid to the carboxy-terminus of the immunoglobulin. Nucleic acid sequences encoding these fusion proteins and methods of their preparation by genetic engineering techniques are also disclosed.

SUMMARY:

BSUM(6)

Another potential problem with expressing proteins, such as the lymphokine LT, as a \*\*fusion\*\* \*\*protein\*\* to an immunoglobulin chain is that the native molecule exists in solution as a trimer and binds more efficiently to. . . amino terminus is required for receptor binding activity. In fact, it has been postulated that the amino and carboxy-termini of \*\*TNF\*\*.varies., and, by analogy, LT, together form a structure that is required for receptor interaction.

DETDESC:

DETD(49)

Ig\*\*TNF\*\* immunoconjugates were made by fusing nucleotide sequences encoding \*\*TNF\*\*.alpha. and immunoglobulin heavy chain such that \*\*TNF\*\*.alpha. is fused to the carboxy terminus of the heavy chain. Briefly, the mature \*\*TNF\*\*.alpha. coding sequence was fused to the end of the human C.gamma.1 CH3 exon using oligonucleotides. The recombined fragment was joined. . . selected as described above. Clones secreting human antibody determinants were expanded and used for the production and purification of the ch14.18-CH3-\*\*TNF\*\*.alpha. \*\*fusion\*\* \*\*protein\*\* by protein A Sepharose chromatography. The activity of the \*\*fusion\*\* \*\*protein\*\* was tested as described above for the CH3-LT fusion proteins.

DETDESC:

DETD(50)

As seen in FIG. 10, the amount of cytotoxicity obtained with the \*\*fusion\*\* \*\*protein\*\* met or exceeded that of native \*\*TNF\*\*.alpha. at either early (20 hr) or late (24 hr) points in the assay. This \*\*fusion\*\* \*\*protein\*\* appears to be fully functional with respect to \*\*TNF\*\*.alpha. activity, even though it was purified using protein A Sepharose. The CH3-LT construct was partially inactivated by the elution at. . .  
=> d ab kwic 9

US PAT NO: 5,712,155 [IMAGE AVAILABLE] L7: 9  
of 47

ABSTRACT:

Tumor necrosis factor receptor DNAs and expression vectors encoding TNF receptors, and processes for producing TNF receptors as products of recombinant cell culture, are disclosed.

DETDESC:

DETD(71)

A. Radiolabeling of \*\*TNF\*\*.alpha. and \*\*TNF\*\*.beta.. Recombinant human \*\*TNF\*\*.alpha., in the form of a \*\*fusion\*\* \*\*protein\*\* containing a hydrophilic octapeptide at the N-terminus, was expressed in yeast as a secreted protein and purified by affinity chromatography (Hopp et al., Bio/Technology 6:1204, 1988). Purified recombinant human \*\*TNF\*\*.beta. was purchased from R&D Systems (Minneapolis, Minn.). Both proteins were radiolabeled using the commercially available solid phase agent, IODO-GEN (Pierce).. . . 20 .mu.l (2 mCi) Na .sup.125 I. This solution was then transferred to a second glass tube containing 5 .mu.g \*\*TNF\*\*.alpha. (or \*\*TNF\*\*.beta.) in 45 .mu.l PBS for 20 minutes at 4.degree. C. The reaction mixture was fractionated by gel filtration on a. . . serum albumin (BSA), 0.2% (w/v) sodium azide and 20 mM Hepes pH 7.4 (binding medium). The final pool of .sup.125 I-\*\*TNF\*\* was diluted to a working stock solution of 1.times.10.sup.-7 M in binding medium and stored for up to one month at 4.degree. C. without detectable loss of receptor binding activity. The specific activity is routinely 1.times.10.sup.6 cpm/mole \*\*TNF\*\*.

=> d ab kwic 7,6,2,1

US PAT NO: 5,716,805 [IMAGE AVAILABLE] L7: 7  
of 47

ABSTRACT:

There is disclosed a method of preparing a soluble mammalian protein by culturing a host cell transformed or transfected with an expression vector encoding a fusion protein comprising a zipper domain and a heterologous mammalian protein.

DETDESC:

DETD(2)

The . . . of preparing a soluble mammalian protein by culturing a host cell transformed or transfected with an expression vector encoding a \*\*fusion\*\* \*\*protein\*\* comprising a zipper domain and a heterologous mammalian protein. In one embodiment, the heterologous mammalian protein comprises an extracellular domain. . . 358:26, 1992; Goodwin et al., Cell 73:447; 1993), which includes CD40 Ligand (CD40-L), CD27 Ligand (CD27-L), OX40 Ligand (OX40-L), and \*\*TNF\*\*. Structural studies of certain members of this family of proteins indicate that they form homotrimers. The inventive method will also. . .

DETDESC:

DETD(4)

In another embodiment, the heterologous mammalian protein comprises a soluble protein such as a cytokine; the resulting \*\*fusion\*\* \*\*protein\*\* forms an oligomer. Cytokines are soluble mediators released by cells during an immune or inflammatory response, which provide antigenically non-specific, intracellular signals that are crucial in regulating physiological processes. \*\*TNF\*\*.alpha., \*\*TNF\*\*.beta. and certain neurotrophins such as nerve growth factor (NGF) belong to the \*\*TNF\*\*/NGF family. Modeling studies of certain members of this family indicate that they are likely to form oligomers (Goh and Porter,. . .

DETDESC:

DETD(53)



This example describes construction of a CD40-L DNA construct to express a soluble CD40-L **\*\*fusion\*\*** **\*\*protein\*\*** referred to as trimeric CD40-L. CD40-L is a type II transmembrane protein found on activated T cells, that acts as. . . now abandoned, the disclosure of which is incorporated by reference herein. CD40-L is a member of the Tumor Necrosis Factor (**\*\*TNF\*\***) family of proteins; several members of this family are believed to exist in trimeric form.

US PAT NO: 5,721,121 [IMAGE AVAILABLE] L7: 6 of 47

ABSTRACT:

The present invention relates to novel process for the preparation of glycoproteins by mammalian cell culture wherein the sialic acid content of the glycoprotein produced is controlled over a broad range of values by manipulating the cell culture environment. The invention provides for processes in which the sialic acid content of the glycoprotein is modified by changes in cell culture parameters which affect cell specific productivity. Preferred embodiments of the invention include cell culture processes in the osmolality of the cell culture is controlled as well as the concentration of a transcription enhancer during the production phase of the cell culture. The invention further provides for novel preparations of soluble type 1 tumor necrosis factor immunoglobulin G1 and their uses in the treatment of inflammatory or immune related disorders.

DETDESC:

DETD(127)

An . . . biological binding assay (ELIBA) was used to quantitate TNFR1-IgG.sub.1 in rat plasma. This assay is based on the ability of **\*\*TNF\*\***-alpha coupled to horseradish peroxidase (**\*\*TNF\*\***-alpha-HRP) to bind to the receptor portion of the TNFR1-IgG.sub.1 **\*\*fusion\*\*** **\*\*protein\*\***. In this assay, Fab fragments of goat antihuman IgGfc coated on wells of microtiter plates were used to capture TNFR1-IgG.sub.1 by interaction with the Fc portion of the molecule. **\*\*TNF\*\***-alpha-HRP was added to the wells and allowed to bind to the receptor portion of the captured TNFR1-IgG.sub.1. Quantification was determined. . .

US PAT NO: 5,741,774 [IMAGE AVAILABLE] L7: 2 of 47

ABSTRACT:

The present invention relates to the use of a cytokine regulatory agent to reduce the severity of rheumatoid arthritis.

SUMMARY:

BSUM(12)

In . . . if the levels of cytokines that contribute to the deleterious effects associated with rheumatoid arthritis could be regulated. For example, **\*\*TNF\*\*** is believed to have a role in rheumatoid arthritis and administration of a soluble **\*\*TNF\*\*** receptor fused to an immunoglobulin Fc domain resulted delayed the onset of an experimentally induced arthritis and resulted in a less severe grade of arthritis in mice. This result suggests that such a **\*\*fusion\*\*** **\*\*protein\*\*** could be useful for reducing the severity of rheumatoid arthritis.

SUMMARY:

BSUM(13)

Unfortunately, a biological material such as a **\*\*TNF\*\*** receptor/Fc domain **\*\*fusion\*\*** **\*\*protein\*\*** can be expensive to prepare in a form that is sufficiently pure for use as a

therapeutic agent. In addition, such a **\*\*fusion\*\*** **\*\*protein\*\*** can present "foreign" epitopes that may induce an undesirable immune response in the treated subject. Such an immune response can decrease the effective concentration of the agent in the treated subject by binding to the **\*\*fusion\*\*** **\*\*protein\*\*** and can be involved in the formation of immune complexes, which can have deleterious effects in the treated subject. Thus,. . .

US PAT NO: 5,744,304 [IMAGE AVAILABLE] L7: 1 of 47

ABSTRACT:

The present invention describes methods of controlling and regulating the inflammatory reaction generated in response to various toxins, immunogens, pathogens and autoimmune insults. The method employs a vector that includes an anti-cytokine protein or antibacterial protein gene under the control of a cytokine responsive promoter. In animal models, adenoviral vectors successfully delivered the vectors to hepatic cells and were subsequently shown to respond only to stimulation by induced cytokines.

SUMMARY:

BSUM(8)

Other . . . have utilized gene therapy methods. For example, using gene transfer vectors in mice (Kolls et al., 1994), researchers constructed a **\*\*chimeric\*\*** **\*\*protein\*\*** capable of binding and neutralizing tumor necrosis factor (**\*\*TNF\*\***). While the desired effect of producing high levels of constitutively produced **\*\*lymphotoxin\*\*** was achieved using this system, it was also reported that the animals were rendered highly susceptible to infection by Listeria. . .

DETDESC:

DETD(112)

Gene . . . non-replicating adenovirus (6.times.10.sup.12 plaque-forming units) or a DNA-liposome complex (10 mg DNA). The encoded antidote protein may be any of **\*\*TNF\*\***-receptor-human immunoglobulin **\*\*fusion\*\*** **\*\*protein\*\***, IL-10, fibrinogen, ACTH, or BPI. To provide multiple recombinant antidote proteins in vivo, more than one kind of vector-antidote protein. . .

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DRWD — Drawing Description

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ECL — Exemplary Claim Number

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FS — Field of Search U.S. Classifications and IPCs

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ICLS — Issue Classification

IN — Inventor Information

IPC — International Classification

OREF — Other Publication References Cited

PARN — Parent Case Text Data

PD — Issue Date

PPDR — Number of Drawing Sheets

PPSP — Number of Specification Pages

PRIR — Foreign Application Priority

PTAN — PCT Number

PTFD — PCT Filing Date

PTPD — PCT Publication Date

PTPN — PCT Publication Number

REI — Reissue Data

REL — Related Application Data

TERM — Term Of Patent

TI — Title

UREF — U. S. Patent References Cited

XA — Assistant Examiner

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US PAT NO: 5,744,304 [IMAGE AVAILABLE] L7: 1  
of 47 TITLE: Inflammation-induced expression of a  
recombinant gene  
=> d his

(FILE 'USPAT' ENTERED AT 15:27:34 ON 01 MAY 1998)  
L1 82 S (IMMUNOGLOBULIN OR IMMUNOGLOBULIN  
OR IG)(W)FUSION L2 0 S L1(P)HCG  
L3 2942 S FUSION PROTEIN  
L4 308 S CHIMERIC PROTEIN  
L5 3093 S L3 OR L4

L6 274 S L5 AND (TNF OR CACHECTIN OR  
LYMPHOTOXIN) L7 47 S L5(P)(TNF OR CACHECTIN  
OR LYMPHOTOXIN)

=> s (glycoprotein hormone) and (lh or hcg or fsh or tsh)

5500 GLYCOPROTEIN  
12970 HORMONE  
95 GLYCOPROTEIN HORMONE  
(GLYCOPROTEIN(W)HORMONE)  
6174 LH  
1358 HCG  
1004 FSH  
881 TSH

L8 57 (GLYCOPROTEIN HORMONE) AND (LH OR  
HCG OR FSH OR TSH)  
=> s l5 and l8

L9 7 L5 AND L8

=> d 1-7

1. 5,744,448, Apr. 28, 1998, Human follicle stimulating  
hormone receptor; Christie Ann Kelton, et al., 514/12;  
424/158.1; 514/841, 843; 530/350 [IMAGE AVAILABLE]

2. 5,736,135, Apr. 7, 1998, Method for making variant  
secreted proteins with altered properties; David V. Goeddel, et  
al., 424/94.64, 94.63; 435/212, 226, 252.3; 536/23.2 [IMAGE  
AVAILABLE]

3. 5,705,478, Jan. 6, 1998, Covalently linked .beta. subunits of  
the glycoprotein hormones as antagonists; Irving Boime, 514/8,  
2; 530/397, 398, 399 [IMAGE AVAILABLE]

4. 5,688,666, Nov. 18, 1997, Growth hormone variants with  
altered binding properties; Steven H. Bass, et al., 435/69.4;  
530/399 [IMAGE AVAILABLE]

5. 5,686,597, Nov. 11, 1997, Thrombin receptor homolog;  
Roger Coleman, et al., 536/23.5; 435/2, 7.21, 69.1, 252.3,  
254.11 [IMAGE AVAILABLE]

6. 5,607,691, Mar. 4, 1997, Compositions and methods for  
enhanced drug delivery; Ron L. Hale, et al., 424/449; 514/1, 2,  
26, 169, 183, 553, 556; 604/20 [IMAGE AVAILABLE]

7. 5,223,408, Jun. 29, 1993, Method for making variant  
secreted proteins with altered properties; David V. Goeddel, et  
al., 435/69.3, 69.4, 69.52, 69.6, 69.7, 172.3, 189, 195, 215,  
216, 226 [IMAGE AVAILABLE]  
=> d ab 6

US PAT NO: 5,607,691 [IMAGE AVAILABLE] L9: 6  
of 7  
ABSTRACT:

The present invention relates to methods of delivering  
pharmaceutical agents across membranes, including the skin  
layer or mucosal membranes of a patient. A pharmaceutical  
agent is covalently bonded to a chemical modifier, via a  
physiologically cleavable bond, such that the membrane  
transport and delivery of the agent is enhanced.

=> s dimerizing fragment

799 DIMERIZING  
31986 FRAGMENT  
L10 0 DIMERIZING FRAGMENT

(DIMERIZING(W)FRAGMENT)

=> s dimerizing

L11 799 DIMERIZING

=> s l11(p)(chimer? or fusion())protien)

3191 CHIMER?

39921 FUSION

55 PROTIEN

L12 2 L11(P)(CHIMER? OR FUSION(W)PROTIEN)

=> d 1,2

1. 5,219,739, Jun. 15, 1993, DNA sequences encoding bVEGF120 and hVEGF121 and methods for the production of bovine and human vascular endothelial cell growth factors, bVEGF.sub.120 and hVEGF.sub.121; Edmund G. Tischer, et al., 435/69.4, 69.1, 320.1; 530/399; 536/23.5, 23.51 [IMAGE AVAILABLE]

2. 5,194,596, Mar. 16, 1993, Production of vascular endothelial cell growth factor; Edmund G. Tischer, et al., 530/399, 350 [IMAGE AVAILABLE]

=> d kwic

US PAT NO: 5,219,739 [IMAGE AVAILABLE] L12:  
1 of 2

DETDISC:

DETD(29)

In order to prepare the \*\*chimeric\*\* growth factors of the invention, a DNA sequence encoding each desired chain is inserted into a suitable expression vector, e.g.. . . (1989) 161(2):851-858. If the correct dimer structure is not obtained by this route, or if the two chains of the \*\*chimera\*\* are synthesized in different hosts, then an example of one means of refolding and \*\*dimerizing\*\* the chains would be to treat the partially-purified or purified chains with guanidine-HCl, Na.sub.2 SO.sub.3 and Na.sub.2 S.sub.4 O.sub.6, as. . .

=> d kwic 2

US PAT NO: 5,194,596 [IMAGE AVAILABLE] L12:  
2 of 2

DETDISC:

DETD(27)

In order to prepare the \*\*chimeric\*\* growth factors of the invention, a DNA sequence encoding each desired chain is inserted into a suitable expression vector, e.g.. . . (1989) 61(2):851-858. If the correct dimer structure is not obtained by this route, or if the two chains of the \*\*chimera\*\* are synthesized in different hosts, then an example of one means of refolding and \*\*dimerizing\*\* the chains would be to treat the partially-purified or purified chains with guanidine-HCl, Na.sub.2 SO.sub.3 and Na.sub.2 S.sub.4 O.sub.6, as. . .

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\*\*\* As of March 23,1998, SRC1, INFO, and EIDDS will no longer be part \*\*\* of the Dialorder service. You may choose another supplier or go \*\*\* to <http://uncweb.carl.org/> to find out about UnCover's complete \*\*\* document ordering service.

\*\*\*

SYSTEM:HOME

Menu System II: D2 version 1.7.8 term=ASCII

\*\*\* DIALOG HOMEBASE(SM) Main Menu \*\*\*

Information:

1. Announcements (new files, free connect time, price changes, etc.)
2. Database, Rates, & Command Descriptions
3. Help in Choosing Databases for Your Topic
4. Customer Services (telephone assistance, training, seminars, etc.)
5. Product Descriptions

# Connections:

6. DIALOG Menus(SM)
7. DIALOG Business Connection(R) and DIALOG Headlines(SM)
8. DIALOG(R) Document Delivery
9. Data Star(R)
10. Other Online Menu Services & Files (MoneyCenter(R), OAG, TNT, etc.)

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/H = Help /L = Logoff /NOMENU = Command

## Mode

Enter an option number to view information or to connect to an online service. Enter a BEGIN command plus a file number to search a database (e.g., B1 for ERIC).

? b 410

01may98 14:44:24 User217743 Session D445.1  
\$0.00 0.003 Hrs FileHomeBase  
\$0.00 Estimated cost FileHomeBase  
\$0.00 Estimated cost this search  
\$0.00 Estimated total session cost 0.003 Hrs.

File 410:Chronolog(R) 1981-1998/May  
(c) 1998 The Dialog Corporation plc

## Set Items Description

? set hi %%;set hi %%

HIGHLIGHT set on as '%%%%'  
%%HIGHLIGHT set on as '%%%'  
? b 411

01may98 14:44:36 User217743 Session D445.2  
\$0.00 0.003 Hrs File410  
\$0.00 Estimated cost File410  
\$0.00 Estimated cost this search  
\$0.00 Estimated total session cost 0.006 Hrs.  
File 411:DIALINDEX(R)

DIALINDEX(R)  
(c) 1998 The Dialog Corporation plc

\*\*\* DIALINDEX search results display in an abbreviated \*\*\*  
format unless you enter the SET DETAIL ON command. \*\*\* ?  
set files biochem

>>> 162 is unauthorized  
>>> 352 is unauthorized  
>>>2 of the specified files are not available  
You have 32 files in your file list.  
(To see banners, use SHOW FILES command)  
? s hybrid()protein()dimer

Your SELECT statement is:  
s hybrid()protein()dimer

Items File

<-----User Break----->

u!

? s (hybrid()protein() or chimeric or fusion())dimer

Your SELECT statement is:  
s (hybrid()protein() or chimeric or fusion())dimer

Items File

>>>Operator "OR" in invalid position  
? s (hybrid()protein or chimeric or fusion())dimer

Your SELECT statement is:  
s (hybrid()protein or chimeric or fusion())dimer

Items File

7 5: BIOSIS PREVIEWS(R)\_1969-1998/Apr W4  
2 156: Toxline(R)\_1965-1998/Feb  
2 348: EUROPEAN PATENTS\_1978-1998/Apr  
W17 2 357: Derwent Biotechnology  
Abs\_1982-1998/May B2 3 399: CA  
SEARCH(R)\_1967-1998/UD=12818  
1 434: Scisearch(R) Cited Ref Sci\_1974-1998/Apr  
W3  
6 files have one or more items; file list includes 32 files.  
? rf

Your last SELECT statement was:  
S (HYBRID()PROTEIN OR CHIMERIC OR  
FUSION())DIMER

Ref Items File

N1 7 5: BIOSIS PREVIEWS(R)\_1969-1998/Apr W4  
N2 3 399: CA SEARCH(R)\_1967-1998/UD=12818  
N3 2 156: Toxline(R)\_1965-1998/Feb  
N4 2 348: EUROPEAN PATENTS\_1978-1998/Apr  
W17 N5 2 357: Derwent Biotechnology  
Abs\_1982-1998/May B2 N6 1 434: Scisearch(R)  
Cited Ref Sci\_1974-1998/Apr W3 N7 0 40:  
Envirolin(R)\_1975-1998/Mar  
N8 0 41: Pollution Abs\_1970-1998/Apr  
N9 0 68: Env.Bib.\_1974-1998/Mar  
N10 0 71: ELSEVIER BIOBASE\_1994-1998/Apr W3  
6 files have one or more items; file list includes 32 files.  
- Enter P or PAGE for more -  
? b n1-n6

01may98 14:47:35 User217743 Session D445.3  
\$1.50 0.050 Hrs File411  
\$1.50 Estimated cost File411  
\$1.50 Estimated cost this search  
\$1.50 Estimated total session cost 0.056 Hrs.

SYSTEM:OS - DIALOG OneSearch  
File 5:BIOSIS PREVIEWS(R) 1969-1998/Apr W4  
(c) 1998 BIOSIS  
File 399:CA SEARCH(R) 1967-1998/UD=12818  
(c) 1998 American Chemical Society  
\*File 399: Use is subject to the terms of your user/customer  
agreement. RANK charge added; see HELP RATES 399.  
File 156:Toxline(R) 1965-1998/Feb  
(c) format only 1998 The Dialog Corporation  
File 348:EUROPEAN PATENTS\_1978-1998/Apr W17  
(c) 1998 EUROPEAN PATENT OFFICE  
\*File 348: \*\*\* All EPO Fulltext data is now online and current!  
\*\*\* New fulltext will be added weekly. See HELP NEWS 348  
for details. File 357:Derwent Biotechnology Abs  
1982-1998/May B2  
(c) 1998 Derwent Publ Ltd  
File 434:Scisearch(R) Cited Ref Sci\_1974-1998/Apr W3  
(c) 1998 Inst for Sci Info

Set Items Description

? s (hybrid()protein or chimeric or fusion)()dimer

159823 HYBRID  
2695994 PROTEIN  
2593 HYBRID(W)PROTEIN  
38452 CHIMERIC  
270152 FUSION  
81897 DIMER  
S1 17 (HYBRID()PROTEIN OR CHIMERIC OR  
FUSION)()DIMER ? rd

>>>Duplicate detection is not supported for File 348.

>>>Records from unsupported files will be retained in the RD  
set. ...completed examining records  
S2 14 RD (unique items)  
? t s2/3,ab/all

>>>No matching display code(s) found in file(s): 399

2/3,AB/1 (Item 1 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
(c) 1998 BIOSIS. All rts. reserv.

14095349 BIOSIS Number: 01095349  
Molecular genetic study of the interaction of Sindbis virus E2  
with Ross River virus E1 for virus budding  
Yao J; Strauss E G; Strauss J H  
Div. Biol. 15629, California Inst. Technol., Pasadena, CA  
91125, USA Journal of Virology 72 (2). 1998. 1418-1423.  
Full Journal Title: Journal of Virology  
ISSN: 0022-538X  
Language: ENGLISH  
Print Number: Biological Abstracts Vol. 105 Iss. 005 Ref.  
067624 Glycoprotein PE2 of Sindbis virus will form a  
heterodimer with glycoprotein E1 of Ross River virus that is  
cleaved to an E2/E1 heterodimer and transported to the cell  
plasma membrane, but this %%%chimeric%%%  
%%%heterodimer%%% fails to interact with Sindbis virus  
nucleocapsids, and very little budding to produce mature  
virus occurs upon infection with chimeric viruses. We have  
isolated in both Sindbis virus E2 and in Ross River virus E1 a  
series of suppressing mutations that adapt these two proteins  
to one another and allow increased levels of chimeric virus  
production. Two adaptive E1 changes in an ectodomain  
immediately adjacent to the membrane anchor and five  
adaptive E2 changes in a 12-residue ectodomain centered  
on Asp-242 have been identified. One change in Ross River  
virus E1 (Gln-411 foward Leu) and one change in Sindbis  
virus E2 (Asp-248 foward Tyr) were investigated in detail.  
Each change individually leads to about a 10-fold increase in  
virus production, and combined the two changes lead to a  
100-fold increase in virus. During passage of a chimeric virus  
containing Ross River virus E1 and Sindbis virus E2, the E2  
change was first selected, followed by the E1 change.  
Heterodimers containing these two adaptive mutations have  
a demonstrably increased degree of interaction with Sindbis  
virus nucleocapsids. In the parental chimera, no interaction  
between heterodimers and capsids was visible at the plasma  
membrane in electron microscopic studies, whereas  
alignment of nucleocapsids along the plasma membrane,  
indicating interaction of heterodimers with nucleocapsids,  
was readily seen in the adapted chimera. The significance of  
these findings in light of our current understanding of  
alphavirus budding is discussed.

2/3,AB/2 (Item 2 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

(c) 1998 BIOSIS. All rts. reserv.

13781813 BIOSIS Number: 99781813  
Synthesis of green fluorescent protein-ricin and monitoring of  
its intracellular trafficking  
Tagge E; Harris B; Burbage C; Hall P; Vesely J; Willingham  
M; Frankel A Hollings Cancer Cent., Room 311, 86 Jonathan  
Lucas St., Charleston, SC 29425, USA  
Bioconjugate Chemistry 8 (5). 1997. 743-750.  
Full Journal Title: Bioconjugate Chemistry  
ISSN: 1043-1802  
Language: ENGLISH  
Print Number: Biological Abstracts Vol. 104 Iss. 010 Ref.  
139417 We performed genetic engineering to fuse  
enhanced green fluorescent protein (EGFP) to the N  
terminus of RTA, expressed the fusion protein in Escherichia  
coli, purified and reassociated EGFP-RTA with plant RTB,  
and purified EGFP-ricin by size exclusion HPLC. The  
%%%fusion%%% heterodimer%%% was able to bind  
galactosides, intoxicate cells, and show strong fluorescence.  
Mammalian cells incubated with EGFP-ricin showed strong  
cell surface fluorescence at 4 degree C and, on incubation at  
37 degree C, distributed initially to endosomes and then to  
Golgi vesicles. Variable sensitivity of mammalian cells to ricin  
and ricin fusion proteins may be due in part to different  
patterns of intracellular routing. Cells were incubated with  
ricin or EGFP-ricin, and inhibition of protein synthesis was  
measured. Human hepatocellular carcinoma Hep3B cells  
were 10-fold more sensitive to ricin and 85-fold more  
sensitive to EGFP-ricin than human epidermoid carcinoma  
KB cells. Epifluorescence microscopy of cells incubated with  
EGFP-ricin showed greater localization of the fluorescence  
signal in the Golgi compartments in Hep3B cells than in KB  
cells. These data support a model requiring a Golgi-dependent  
step in cell intoxication by ricin. The work further identifies the  
usefulness of green fluorescent protein fusions in the study  
of retrograde transport of internalized peptides.

2/3,AB/3 (Item 3 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
(c) 1998 BIOSIS. All rts. reserv.

13404844 BIOSIS Number: 99404844  
The leucine zipper domain controls the orientation of AP-1 in  
the NFAT cntdot AP-1 cntdot DNA complex  
Erlanson D A; Chytil M; Verdine G L  
Dep. Chem. Chem. Biol., Harvard Univ., Cambridge, MA  
02138, USA Chemistry & Biology (London) 3 (12). 1996.  
981-991.  
Full Journal Title: Chemistry & Biology (London)  
ISSN: 1074-5521  
Language: ENGLISH  
Print Number: Biological Abstracts Vol. 103 Iss. 006 Ref.  
076987 Background: Heterologous transcription factors  
bound to adjacent sites in eukaryotic promoters often exhibit  
cooperative behavior. In most instances, the molecular basis  
for this cooperativity is poorly understood. Our efforts have  
been directed toward elucidation of the mechanism of  
cooperativity between NFAT and AP-1, two proteins that  
coordinately direct expression of the T-cell growth factor  
interleukin-2 (IL-2). Results: We have previously shown that  
NFAT1 orients the two subunits of AP-1, c-Jun and c-Fos, on  
DNA through direct protein sbd protein interactions. In the  
present study, we have constructed cJun sbd cFos chimeric  
proteins and determined their orientation using a novel  
affinity-cleavage technology based on chemical ligation. We  
find that, in the presence of NFAT, the %%%chimeric%%%  
%%%heterodimer%%% binds in such a way as to preserve

the orientation of the AP-1 leucine zipper, but not that of the basic region. Conclusions: Protein-protein interactions between NFAT and the leucine zipper of AP-1 enable the two proteins to bind DNA cooperatively and coordinately regulate the IL-2 promoter. The chemical ligation technology presented here provides a powerful strategy for affinity cleavage studies, including those using recombinant proteins.

2/3,AB/4 (Item 4 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
(c) 1998 BIOSIS. All rts. reserv.

11517100 BIOSIS Number: 98117100

Modulation of cell adhesion by changes in alpha-L beta-2 (LFA-1, CD11a-CD18) cytoplasmic domain-cytoskeleton interaction

Peter K; O'Toole T E  
Innere Med. III, Univ. Heidelberg, Bergheimerstr. 58, 69115 Heidelberg, Germany

Journal of Experimental Medicine 181 (1). 1995. 315-326.

Full Journal Title: Journal of Experimental Medicine

ISSN: 0022-1007

Language: ENGLISH

Print Number: Biological Abstracts Vol. 099 Iss. 006 Ref.

073657 The integrin alpha-L beta-2 (leukocyte function-associated molecule 1, CD11a/CD18) mediates activation-dependent adhesion of leukocytes. The cytoplasmic domains of alpha-L beta-2 have been demonstrated to modulate adhesiveness of alpha-L beta-2. Affinity changes of alpha-L beta-2 for its ligand or postreceptor events can be responsible for this modulation of adhesiveness. To investigate the possible role of the alpha-L beta-2 cytoplasmic domains in postreceptor events we constructed cDNA encoding chimeric proteins with intracellular alpha-L beta-2 domains, which are responsible for alpha-L beta-2 specific intracellular interactions, and extracellular alpha-IIB beta-3 (GP IIb/IIIa) domains, which allow the assessment of the receptor affinity state. The cDNA was stably transfected in Chinese hamster ovary cells and %%%chimeric%%% %%%heterodimer%%% formation proven by immunoprecipitations and flow cytometry. The chimeric receptors mediate adhesion to immobilized fibrinogen, and this adhesion is increased by phorbol myristate acetate and abolished by cytochalasin D. However, neither treatment affects the affinity state of the chimeric receptor, suggesting involvement of the cytoskeleton in the regulation of alpha-L beta-2 mediated cell adhesion. To exclude the possibility of postoccupancy affinity changes of the chimeric receptors, we locked the receptors into a high affinity state by creating a deletion variant. The region deleted (VGFFK) is highly conserved in integrin alpha subunit cytoplasmic domains. Cotransfection of this deletion variant with a beta subunit truncation (beta-3 DELTA-274) and a triple mutation at 758-760 (TTT to AAA) of beta-2 abolishes adhesion without changing the affinity state. A single mutation (TTT to TAT) reduces adhesion by half without affinity change. Scanning electron microscopy reveals impaired spreading of these truncated/mutated chimeras.

Immunofluorescence microscopy demonstrates a correlation between impaired adhesion and a decrease in the ability to form focal adhesions and to organize the cytoskeleton into stress fibers. These results describe the integrin/cytoskeleton interaction, the organization of the cytoskeleton, and cell spreading as postreceptor events modulating alpha-L beta-2 cytoplasmic domain mediated cell adhesion. Furthermore, we demonstrate that the cytoplasmic domain of the beta-2 subunit, and within it the TTT region, are required for these postreceptor events. Additionally, we present a new

approach, using deletion variants to lock integrins in a high affinity state without interfering with the investigated integrin/cytoskeleton interaction. This approach may be generally useful to investigate the role of postreceptor events in integrin-mediated cell adhesion and migration.

2/3,AB/5 (Item 5 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
(c) 1998 BIOSIS. All rts. reserv.

11444145 BIOSIS Number: 98044145

A general method for facilitating heterodimeric pairing between two proteins: Application to expression of alpha and beta T-cell receptor extracellular segments

Chang H-C; Bao Z-Z; Yao Y; Tse A G D; Goyarts E C; Madsen M; Kawasaki E; Brauer P P; Sacchetti J C; Nathenson S G; Reinherz E L

Lab. Immunobiology, Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA 02115, USA

Proceedings of the National Academy of Sciences of the United States of America 91 (24). 1994. 11408-11412.

Full Journal Title: Proceedings of the National Academy of Sciences of the United States of America

ISSN: 0027-8424

Language: ENGLISH

Print Number: Biological Abstracts Vol. 099 Iss. 003 Ref.

028689 Generation of soluble T-cell receptor (TCR) molecules by a variety of genetic engineering methods has been hampered by inefficient pairing of alpha and beta subunits in the absence of their respective transmembrane regions and associated CD3 components. To overcome this obstacle, we have added 30-amino acid-long segments to the carboxyl termini of alpha and beta extracellular domains via a cleavable flexible linker. These peptide segments (BASE-p1 for alpha and ACID-p1 for beta) have been previously shown to selectively associate to form a stable heterodimeric coiled coil termed a leucine zipper. Homodimeric structures are not permitted due to electrostatic repulsion among amino acid side chains. Expression of a representative TCR-leucine zipper fusion protein in a baculovirus expression system results in production of alpha-beta TCR heterodimer at 0.6-1.4 mg/liter. This yield is 5- to 10-fold greater than that of the TCR expressed in the absence of the synthetic leucine zipper sequence. The structure of the TCR component of the %%%fusion%%% %%%heterodimer%%% was judged to be native when probed with a panel of 17 mAbs specific for a and B constant and variable domains. A mAb specific for the isolated BASE-p1/ACID-p1 coiled coil was also generated and shown to react with the TCR fusion protein. The above technology should be broadly useful in the efficient production and purification of TCRs as well as other heterodimeric proteins.

2/3,AB/6 (Item 6 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
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10131310 BIOSIS Number: 95131310

SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR INHIBITION OF HUMAN IMMUNODEFICIENCY VIRUS ACTIVATION

HOWARD O M Z; CLOUSE K A; SMITH C; GOODWIN R G; FARRAR W L LAB. MOL. IMMUNOREGULATION, BIOL. RES. MODIFIERS PROGRAM, NATIONAL CANCER INST.-FREDERICK CANCER RES. DEVELOPMENT CENTER, PO BOX B, FREDERICK, MD 21702, USA.

PROC NATL ACAD SCI U S A 90 (6). 1993. 2335-2339.

CODEN: PNASA Full Journal Title: Proceedings of the  
National Academy of Sciences of the United States of America  
Language: ENGLISH

The inflammatory cytokine tumor necrosis factor .alpha.  
(TNF-.alpha.) has been shown to stimulate human  
immunodeficiency virus type 1 (HIV-1) replication in both  
chronically and acutely infected T lymphocytes and  
monocytes. Transcriptional activation of the HIV long terminal  
repeat and subsequent increase in virus production are linked  
to TNF activation of the cellular transcription factor  
NF-.kappa.B. Here we report the use of two forms of soluble  
recombinant type 1 (p80) TNF receptor to inhibit  
TNF-induced HIV activation in vitro. One receptor form is  
a monomer containing the entire 236 residues of the  
extracellular (ligand-binding) portion of p80. A second receptor  
form is a %%%chimeric%%% %%%homodimer%%%  
containing these residues fused to a truncated human IgG1  
immunoglobulin heavy chain and, thus, resembles a bivalent  
antibody without light chains. These recombinant receptor  
proteins were tested for their ability to inhibit  
TNF-.alpha.-induced expression of HIV-1 in chronically  
infected human cell lines. We also examined the ability of the  
soluble receptors to limit the activation of the HIV-long  
terminal repeat transcription. The soluble TNF receptor  
dimer was most effective at blocking  
TNF-.alpha.-induced HIV-1 expression in both monocytoid and  
lymphoid cells. The molar ratio of TNF-receptor dimer to  
TNF-.alpha. found to be most effective was, at least, 5:1.  
We conclude that at specific TNF/soluble TNF-receptor dimer  
ratios, TNF-.alpha.-induced HIV-1 transcription and  
expression can be limited in vitro.

2/3,AB/7 (Item 7 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
(c) 1998 BIOSIS. All rts. reserv.

7316687 BIOSIS Number: 38097208  
RECOMBINANT DHFR %%%FUSION%%  
%%DIMER%%  
IWAKURA M; MATTHEWS C R  
DEP. CHEM., PA. STATE UNIV., UNIVERSITY PARK, PA.  
16802. THIRTY-FOURTH ANNUAL MEETING OF THE  
BIOPHYSICAL SOCIETY, BALTIMORE, MARYLAND, USA,  
FEBRUARY 18-22, 1990. BIOPHYS J 57 (2 PART 2). 1990.  
436A. CODEN: BIOJA  
Language: ENGLISH  
Document Type: CONFERENCE PAPER

2/3,AB/8 (Item 1 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
(c) 1998 American Chemical Society. All rts. reserv.

122127577 CA: 122(11)127577m PATENT  
Biologically active polypeptide fusion dimers.  
INVENTOR(AUTHOR): Thomason, Arlen R.  
LOCATION: USA  
ASSIGNEE: Amgen Inc.  
PATENT: European Pat. Appl. ; EP 618227 A1 DATE:  
941005 APPLICATION: EP 94105075 (940331) \*US 41635  
(930401)  
PAGES: 30 pp. CODEN: EPXXDW LANGUAGE: English  
CLASS: C07K-015/00A; C07K-013/00B; C12N-015/12B;  
C12N-015/18B; A61K-037/36B  
DESIGNATED COUNTRIES: AT; BE; CH; DE; DK; ES; FR;  
GB; GR; IE; IT; LI; LU; MC; NL; PT; SE

2/3,AB/9 (Item 2 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
(c) 1998 American Chemical Society. All rts. reserv.

121173277 CA: 121(15)173277r JOURNAL  
Properties of permease dimer, a fusion protein containing two  
lactose permease molecules from Escherchia coli  
AUTHOR(S): Sahin-Toth, Miklos; Lawrence, Mary C.;  
Kaback, H. Ronald LOCATION: Howard Hughes Med. Inst.,  
Univ. California, Los Angeles, CA, 90024-1662, USA  
JOURNAL: Proc. Natl. Acad. Sci. U. S. A. DATE: 1994  
VOLUME: 91 NUMBER: 12 PAGES: 5421-5 CODEN:  
PNASA6 ISSN: 0027-8424 LANGUAGE: English

2/3,AB/10 (Item 3 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
(c) 1998 American Chemical Society. All rts. reserv.

121033159 CA: 121(3)33159d PATENT  
A subpopulation of Mac-1 (CD11b/CD18) molecules which  
mediate neutrophil adhesion to ICAM-1 and fibrinogen and its  
monoclonal antibodies INVENTOR(AUTHOR): Diamond,  
Michael; Springer, Timothy A. LOCATION: USA  
ASSIGNEE: Center for Blood Research  
PATENT: PCT International ; WO 9408620 A1 DATE:  
940428  
APPLICATION: WO 93US9777 (931012) \*US 958904  
(921009) \*US 964156 (921022) PAGES: 119 pp. CODEN:  
PIXXD2 LANGUAGE: English CLASS: A61K-039/395A;  
C07K-015/28B DESIGNATED COUNTRIES: AU; CA; JP;  
KR DESIGNATED REGIONAL: AT ; BE; CH; DE; DK; ES;  
FR; GB; GR; IE; IT; LU; MC; NL; PT; SE

2/3,AB/11 (Item 1 from file: 348)  
DIALOG(R)File 348:EUROPEAN PATENTS  
(c) 1998 EUROPEAN PATENT OFFICE. All rts. reserv.

00636901  
ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 Biologically active polypeptide fusion  
dimers.  
Biologisch aktive Polypeptid Fusionsdimere.  
Dimeres de fusionspolypeptidiques biologiquement actifs.  
PATENT ASSIGNEE:  
AMGEN INC., (923233), Amgen Center, 1840 Dehavilland  
Drive, Thousand Oaks, CA 91320-1789, (US), (applicant  
designated states:  
AT;BE;CH;DE;DK;ES;FR;GB;GR;IE;IT;LI;LU;MC;NL;PT;SE)  
INVENTOR:  
Thomason, Arlen R., 2298 Watertown Court, Thousand  
Oaks, CA 91380, (US) LEGAL REPRESENTATIVE:  
Vossius, Volker, Dr. et al (12524), Dr. Volker Vossius  
Patentanwaltskanzlei - Rechtsanwaltskanzlei Holbeinstrasse  
5, D-81679 Munchen, (DE)  
PATENT (CC, No, Kind, Date): EP 618227 AT 941005  
(Basic) APPLICATION (CC, No, Date): EP 94105075  
940331  
PRIORITY (CC, No, Date): US 41635 930401  
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB;  
GR; IE; IT; LI; LU; MC; NL; PT; SE  
INTERNATIONAL PATENT CLASS: C07K-015/00;  
C07K-013/00; C12N-015/12; C12N-015/18; A61K-037/36;

#### ABSTRACT EP 618227 A1

The present invention provides a biologically active  
multimeric polypeptide molecule in which two or more  
monomeric subunits are linked together as a single  
polypeptide ("fusion multimer"). These fusion multimers are

more easily and rapidly refolded than unfused multimers, because the reactions necessary to generate the biologically active multimeric form of the polypeptide proceed with first order, rather than second or higher order, reaction kinetics. Fusion multimers also eliminate the simultaneous formation of undesired polypeptide by-products during refolding. The fusion multimers of the present invention specifically include PDGF fusion dimers.

ABSTRACT WORD COUNT: 91

LANGUAGE (Publication,Procedural,Application): English;  
English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS A (English) EPABF2 501

SPEC A (English) EPABF2 8793

Total word count - document A 9294

Total word count - document B 0

Total word count - documents A + B 9294

2/3,AB/12 (Item 2 from file: 348)

DIALOG(R)File 348:EUROPEAN PATENTS

(c) 1998 EUROPEAN PATENT OFFICE. All rts. reserv.

00450411

ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 PRODUCTION OF VASCULAR  
ENDOTHELIAL CELL GROWTH FACTOR

HERSTELLUNG DES VASKULAREN ENDOTHELIALEN

ZELLWACHSTUMSFAKTORS PRODUCTION DE

FACTEUR DE CROISSANCE DE CELLULES

ENDOTHELIALES VASCULAIRES PATENT ASSIGNEE:

SCIOS NOVA INC., (1619850), 2450 Bayshore Parkway,  
Mountain View, CA 94043, (US), (applicant designated  
states:

AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;LU;NL;SE)

INVENTOR:

TISCHER, Edmund, G., 3316 Kenneth Drive, Palo Alto, CA  
94303, (US) ABRAHAM, Judith, A., 655 S. Fair Oaks Avenue,  
207, Sunnyvale, CA 94086, (US)

FIDDES, John, C., 2320 Bryant Street, Palo Alto, CA 94301,

(US) MITCHELL, Richard, L., 15920, 177th Avenue NE,  
Woodinville Washington 98072, (US)

LEGAL REPRESENTATIVE:

Goldin, Douglas Michael et al (31061), J.A. KEMP & CO. 14,  
South Square Gray's Inn, London WC1R 5LX, (GB)

PATENT (CC, No, Kind, Date): EP 484401 A1 920513

(Basic) EP 484401 A1 920819

EP 484401 B1 960911

WO 9102058 910221

APPLICATION (CC, No, Date): EP 90911525 900727; WO

90US4227 900727 PRIORITY (CC, No, Date): US 387545

890727; US 450883 891214 DESIGNATED STATES: AT;

BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE

INTERNATIONAL PATENT CLASS: C12N-015/12;

C12N-015/18; C12N-005/10; A61K-038/27;

LANGUAGE (Publication,Procedural,Application): English;

English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS B (English) EPAB96 1760

CLAIMS B (German) EPAB96 1678

CLAIMS B (French) EPAB96 1929

SPEC B (English) EPAB96 23518

Total word count - document A 0

Total word count - document B 28885

Total word count - documents A + B 28885

2/3,AB/13 (Item 1 from file: 357)

DIALOG(R)File 357:Derwent Biotechnology Abs

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172040 DBA Accession No.: 94-14591 PATENT

Multimeric fusion protein production - human single chain  
platelet-derived growth factor-B or -A, vascular endothelial  
cell growth factor, placental growth factor or platelet-derived  
growth factor-inhibitor gene cloning

PATENT ASSIGNEE: Amgen 1994

PATENT NUMBER: EP 618227 PATENT DATE: 941005

WPI ACCESSION NO.: 94-304405 (9438)

PRIORITY APPLIC. NO.: US 41635 APPLIC. DATE: 930401

NATIONAL APPLIC. NO.: EP 94105075 APPLIC. DATE:

940331

LANGUAGE: English

ABSTRACT: A new protein comprises 2 or more  
polypeptide subunits of a naturally occurring multimer,  
incorporated head-to-tail in a single continuous polypeptide.  
The protein is preferably a single chain platelet-derived  
growth factor (PDGF) family multimer. PDGF-A, PDGF-B,  
vascular endothelial cell growth factor or placental growth  
factor sequences may be used, especially a  
109-amino-acid and/or a 119-amino-acid cleavage product  
of human PDGF-B. A PDGF-BB %%%fusion%%  
%%dimer%% is claimed. The fusion protein may be  
expressed in a transfected host cell. A fusion protein as  
above with PDGF-inhibitor activity has at least 1  
biologically inactive subunit and 1 active subunit. The fusion  
multimers are more easily and rapidly refolded than unfused  
multimers, since the reactions necessary to generate the  
biologically active multimeric form proceed with 1st-order  
rather than 2nd-order kinetics. In addition, simultaneous  
formation of undesired byproducts during refolding is  
avoided. The subunits may be linked directly or via a spacer.  
(30pp)

2/3,AB/14 (Item 2 from file: 357)

DIALOG(R)File 357:Derwent Biotechnology Abs

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120050 DBA Accession No.: 91-07692

Isolation of active homodimers of HIV-1 reverse-transcriptase  
by the application of a genetically engineered metal binding  
peptide - HIV virus-1 reverse-transcriptase with metal  
binding affinity tail; enzyme purification from Escherichia coli  
by metal chelate affinity chromatography (conference  
abstract)

AUTHOR: Chattopadhyay D; Evans D B; Deibel Jr M R;  
Einspahr H M; Sharma S K

CORPORATE AFFILIATE: Upjohn

CORPORATE SOURCE: Upjohn Laboratories, Kalamazoo,  
Michigan 49001, USA. JOURNAL: Abstr.Pap.Am.Chem.Soc.  
(201 Meet., Pt.1, BIOT4) 1991 CODEN: ACSRAL

LANGUAGE: English

ABSTRACT: A metal binding peptide was engineered onto the  
N-terminus of HIV virus-1 reverse-transcriptase (RT,  
EC-2.7.7.49) for specific and rapid isolation by metal  
chelate affinity chromatography (immobilized metal affinity  
chromatography). A recombinant fusion protein from a crude  
Escherichia coli extract was bound to an immobilized nickel  
column. Most of the contaminating E. coli proteins were  
eluted with 35 mM-100 mM imidazole, and the bound  
fusion protein was eluted with 300 mM imidazole. The  
peptide eluting later was in a form that migrated on  
SDS-PAGE predominantly as a 66 kDa polypeptide. HPLC  
was carried out in conjunction with assays of RT and  
RNA-ase-H activities to define the nature of the 66 kDa  
protein. Results indicated that the isolated 66 kDa HIV virus



RT can be resolved into active homodimers (70%) and (presumably) inactive monomers (30%). Preparation of a similar %%%chimeric%%%heterodimer%%% (p66/p51) was presented. (0 ref) ? s leucine()zipper

87334 LEUCINE  
10114 ZIPPER  
S3 8820 LEUCINE()ZIPPER  
? s glycoprotein()hormone

187148 GLYCOPROTEIN  
775094 HORMONE  
S4 2225 GLYCOPROTEIN()HORMONE  
? s s4 and s3

2225 S4  
8820 S3  
S5 20 S4 AND S3  
? rd

>>>Duplicate detection is not supported for File 348.

>>>Records from unsupported files will be retained in the RD set. ...completed examining records

S6 17 RD (unique items)  
? s s6 not s2

17 S6  
14 S2  
S7 17 S6 NOT S2  
? ds

Set	Items	Description
S1	17	(HYBRID()PROTEIN OR CHIMERIC OR FUSION()DIMER S2 14 RD (unique items)
S3	8820	LEUCINE()ZIPPER
S4	2225	GLYCOPROTEIN()HORMONE
S5	20	S4 AND S3
S6	17	RD (unique items)
S7	17	S6 NOT S2

? t s7/6/all

7/6/1 (Item 1 from file: 5)  
11619186 BIOSIS Number: 98219186  
Upstream stimulatory factor, a basic-helix-loop-helix-zipper protein, regulates the activity of the alpha-%%glycoprotein%%% hormone%%% subunit gene in pituitary cells  
Print Number: Biological Abstracts Vol. 099 Iss. 010 Ref. 141362

7/6/2 (Item 2 from file: 5)  
10403549 BIOSIS Number: 96003549  
MODIFICATION OF DNA TOPOISOMERASE II ACTIVITY VIA DIRECT INTERACTIONS WITH THE CYCLIC ADENOSINE-3' 5'-MONOPHOSPHATE RESPONSE ELEMENT-BINDING PROTEIN AND RELATED TRANSCRIPTION FACTORS

7/6/3 (Item 1 from file: 434)  
15904748 Genuine Article#: BJ31P Number of References: 140 Title: The gonadotropin genes: Evolution of distinct mechanisms for hormonal control (ABSTRACT AVAILABLE)

7/6/4 (Item 2 from file: 434)  
15391039 Genuine Article#: WD804 Number of References: 193 Title: Structural and functional diversity in the leucine rich repeat family of proteins

7/6/5 (Item 3 from file: 434)  
11855529 Genuine Article#: JR313 Number of References: 63 Title: MUTUAL CROSS-INTERFERENCE BETWEEN GLUCOCORTICOID RECEPTOR AND CREB INHIBITS TRANSACTIVATION IN PLACENTAL CELLS

7/6/6 (Item 4 from file: 434)  
11648171 Genuine Article#: HZ964 Number of References: 34 Title: ANALYSIS OF DNA-SEQUENCES REQUIRED FOR PITUITARY-SPECIFIC EXPRESSION OF THE %%%GLYCOPROTEIN%%% hormone%%% ALPHA-SUBUNIT GENE (Abstract Available)

7/6/7 (Item 5 from file: 434)  
11589134 Genuine Article#: HV306 Number of References: 43 Title: DEOXYRIBONUCLEASE-HYPERSENSITIVE SITES IN THE %%%GLYCOPROTEIN%%% hormone%%% ALPHA-SUBUNIT GENE FROM TROPHOBLASTIC AND NONTROPHOBLASTIC HUMAN TUMOR-CELL LINES - CORRELATION WITH EXPRESSION AND EFFECT OF CHEMICAL INDUCERS (Abstract Available)

7/6/8 (Item 6 from file: 434)  
11541835 Genuine Article#: HQ338 Number of References: 57 Title: TISSUE-SPECIFIC GENE-EXPRESSION IN THE PITUITARY - THE %%%GLYCOPROTEIN%%% hormone%%% ALPHA-SUBUNIT GENE IS REGULATED BY A GONADOTROPE-SPECIFIC PROTEIN (Abstract Available)

7/6/9 (Item 7 from file: 434)  
11158395 Genuine Article#: GL704 Number of References: 51 Title: THE GENE ENCODING OVINE FOLLICLE-STIMULATING HORMONE-BETA - ISOLATION, CHARACTERIZATION, AND COMPARISON TO A RELATED OVINE GENOMIC SEQUENCE (Abstract Available)

7/6/10 (Item 8 from file: 434)  
11148013 Genuine Article#: GL389 Number of References: 42 Title: BINDING-SPECIFICITY OF CYCLIC ADENOSINE 3',5'-MONOPHOSPHATE-RESPONSIVE ELEMENT (CRE)-BINDING PROTEINS AND ACTIVATING TRANSCRIPTION FACTORS TO NATURALLY-OCCURRING CRE SEQUENCE VARIANTS (Abstract Available)

7/6/11 (Item 9 from file: 434)  
11114683 Genuine Article#: GH333 Number of References: 59 Title: EXPRESSION OF LUTEINIZING HORMONE-BETA SUBUNIT CHLORAMPHENICOL ACETYLTRANSFERASE (LH-BETA-CAT) FUSION GENE IN RAT PITUITARY-CELLS - INDUCTION BY CYCLIC 3'-ADENOSINE MONOPHOSPHATE (CAMP) (Abstract Available)

7/6/12 (Item 10 from file: 434)  
11035692 Genuine Article#: GB640 Number of References:  
36 Title: THE GENE FOR THE COMMON ALPHA-SUBUNIT  
OF PORCINE PITUITARY %%%GLYCOPROTEIN%%  
%%HORMONE%% (Abstract Available)

7/6/13 (Item 11 from file: 434)  
10914215 Genuine Article#: FR684 Number of References:  
44 Title: AMINO-TERMINAL LEUCINE-RICH REPEATS IN  
GONADOTROPIN RECEPTORS DETERMINE  
HORMONE SELECTIVITY (Abstract Available)

7/6/14 (Item 12 from file: 434)  
10812386 Genuine Article#: FJ155 Number of References:  
109 Title: STRUCTURE OF THE GENE ENCODING VGF, A  
NERVOUS SYSTEM-SPECIFIC MESSENGER-RNA  
THAT IS RAPIDLY AND SELECTIVELY INDUCED BY  
NERVE GROWTH-FACTOR IN PC12 CELLS (Abstract  
Available)

7/6/15 (Item 13 from file: 434)  
10710886 Genuine Article#: FA907 Number of References:  
52 Title: EVOLUTION OF PLACENTA-SPECIFIC  
GENE-EXPRESSION - COMPARISON OF THE EQUINE  
AND HUMAN GONADOTROPIN ALPHA-SUBUNIT GENES  
(Abstract Available)

7/6/16 (Item 14 from file: 434)  
10613191 Genuine Article#: ET529 Number of References:  
35 Title: DIFFERENT COMBINATIONS OF REGULATORY  
ELEMENTS MAY EXPLAIN WHY PLACENTA-SPECIFIC  
EXPRESSION OF THE %%%GLYCOPROTEIN%%  
%%HORMONE%% ALPHA-SUBUNIT GENE  
OCCURS ONLY IN PRIMATES AND HORSES (Abstract  
Available)

7/6/17 (Item 15 from file: 434)  
10592009 Genuine Article#: EQ593 Number of References:  
56 Title: ROLE OF ERYTHROPOIETIN IN ADAPTATION TO  
HYPOXIA (Abstract Available )  
? s hcg or fsh or lh or tsh or inhibin

22735 HCG  
45501 FSH  
77174 LH  
37464 TSH  
11209 INHIBIN

S8 155289 HCG OR FSH OR LH OR TSH OR INHIBIN  
? ds

Set	Items	Description
S1	17	(HYBRID()PROTEIN OR CHIMERIC OR FUSION)()DIMER S2 14 RD (unique items)
S3	8820	LEUCINE()ZIPPER
S4	2225	GLYCOPROTEIN()HORMONE
S5	20	S4 AND S3
S6	17	RD (unique items)
S7	17	S6 NOT S2
S8	155289	HCG OR FSH OR LH OR TSH OR INHIBIN
? s s8 and dimerize		

155289 S8

1116 DIMERIZE

S9 9 S8 AND DIMERIZE  
? rd

>>>Duplicate detection is not supported for File 348.

>>>Records from unsupported files will be retained in the RD  
set. ...completed examining records  
S10 7 RD (unique items)  
? t s10/6/all

10/6/1 (Item 1 from file: 5)  
13453884 BIOSIS Number: 99453884  
Familial congenital hypothyroidism caused by abnormal and  
bioinactive %%%TSH%% due to mutations in the  
beta-subunit gene  
Print Number: Biological Abstracts Vol. 103 Iss. 008 Ref.  
109553

10/6/2 (Item 2 from file: 5)  
11215457 BIOSIS Number: 97415457  
Kinetics of Fc-epsilon-R1 dimer formation by specific  
monoclonal antibodies on mast cells  
Print Number: Biological Abstracts Vol. 098 Iss. 007 Ref.  
086269

10/6/3 (Item 1 from file: 348)  
00446329  
ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 MODIFIED FORMS OF  
REPRODUCTIVE HORMONES  
MODIFIZIERTE FORMEN VON  
FORTPFLANZUNGSHORMONEN  
FORMES MODIFIEES D'HORMONES DE REPRODUCTION  
LANGUAGE (Publication,Procedural,Application): English;  
English; English FULLTEXT AVAILABILITY:  
Available Text Language Update Word Count  
CLAIMS B (English) EPAB97 1254  
CLAIMS B (German) EPAB97 1187  
CLAIMS B (French) EPAB97 1421  
SPEC B (English) EPAB97 9420  
Total word count - document A 0  
Total word count - document B 13282  
Total word count - documents A + B 13282

10/6/4 (Item 2 from file: 348)  
00212605  
ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 Substrate formulation in  
2-amino-2-methyl-1-propanol buffer for alkaline phosphatase  
assays.  
Substratenansatz von Mischungen in einem  
2-Amino-2-methyl-1-propanol enthaltenden Puffer fur  
Alkalin-Phosphatase-Probe.  
Formulation des substrats dans un tampon de  
2-amino-2-methyle-1-propanol pour les essais  
d'alkaline-phosphatase.  
LANGUAGE (Publication,Procedural,Application): English;  
English; English FULLTEXT AVAILABILITY:  
Available Text Language Update Word Count  
CLAIMS B (English) EPBBF1 711  
CLAIMS B (German) EPBBF1 669  
CLAIMS B (French) EPBBF1 761  
SPEC B (English) EPBBF1 4575  
Total word count - document A 0  
Total word count - document B 6716  
Total word count - documents A + B 6716

10/6/5 (Item 1 from file: 357)  
111947 DBA Accession No.: 90-14638

Modified forms of %%%FSH%%%, %%%LH%%%,  
%%HCG%% and thyrotropin - efficiently produced and  
secreted in recombinant mammal cell culture; altered  
glycosylation and activity

10/6/6 (Item 1 from file: 434)  
15617755 Genuine Article#: WU995 Number of References:  
32 Title: Crystal chemistry of the copper bromide  
2-aminopyrimidine system ( ABSTRACT AVAILABLE)

10/6/7 (Item 2 from file: 434)  
15555858 Genuine Article#: WQ020 Number of  
References: 73 Title: Metalloporphyrin mixed-valence pi-cation  
radicals: Solution stability and properties (ABSTRACT  
AVAILABLE)  
? t s10/3,ab/3,5

>>>No matching display code(s) found in file(s): 399

10/3,AB/3 (Item 1 from file: 348)  
DIALOG(R)File 348:EUROPEAN PATENTS  
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00446329  
ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 MODIFIED FORMS OF  
REPRODUCTIVE HORMONES  
MODIFIZIERTE FORMEN VON  
FORTPFLANZUNGSHORMONEN  
FORMES MODIFIEES D'HORMONES DE REPRODUCTION  
PATENT ASSIGNEE:  
WASHINGTON UNIVERSITY, (645444), Campus Box 1054,  
One Brookings Hall, St. Louis, MO 63130, (US), (applicant  
designated states:

AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;LU;NL;SE)  
INVENTOR:  
BOIME, Irving, 270 Oak Park Drive, St. Louis, MO 63141,  
(US) MATZUK, Martin, M., One Baylor Hospital Plaza,  
College of Medicine, Houston, TX 7703012, (US)  
KEENE, Jeffrey, L., 8100 Leafland Court, St. Louis, MO  
63123, (US) LEGAL REPRESENTATIVE:  
Goldin, Douglas Michael et al (31061), J.A. KEMP & CO. 14,  
South Square Gray's Inn, London WC1R 5LX, (GB)  
PATENT (CC, No, Kind, Date): EP 461200 A1 911218  
(Basic) EP 461200 A1 921119

EP 461200 B1 970122  
WO 9009800 900907  
APPLICATION (CC, No, Date): EP 90905115 900220; WO  
90US1037 900220 PRIORITY (CC, No, Date): US 313646  
890221

DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB;  
IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS:  
C12P-021/00; C12P-021/02; C07K-014/59; A61K-038/24;  
LANGUAGE (Publication,Procedural,Application): English;  
English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS B (English) EPAB97 1254  
CLAIMS B (German) EPAB97 1187  
CLAIMS B (French) EPAB97 1421  
SPEC B (English) EPAB97 9420

Total word count - document A 0  
Total word count - document B 13282  
Total word count - documents A + B 13282

10/3,AB/5 (Item 1 from file: 357)  
DIALOG(R)File 357:Derwent Biotechnology Abs

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111947 DBA Accession No.: 90-14638 PATENT  
Modified forms of %%%FSH%%%, %%%LH%%%,  
%%HCG%% and thyrotropin - efficiently produced and  
secreted in recombinant mammal cell culture; altered  
glycosylation and activity  
PATENT ASSIGNEE: Washington-Univ. 1990  
PATENT NUMBER: WO 9009800 PATENT DATE: 900907  
WPI ACCESSION NO.: 90-290155 (9038)  
PRIORITY APPLIC. NO.: US 313646 APPLIC. DATE:  
890221  
NATIONAL APPLIC. NO.: WO 90US1037 APPLIC. DATE:  
900220  
LANGUAGE: English  
ABSTRACT: A modified %%%LH%%% beta subunit is  
claimed having enhanced activity to %%%dimerize%%%  
with the alpha subunit and enhanced secretion as a dimer  
from mammalian recombinant host cells. The subunit is a  
modified beta-subunit where the 7 amino acid hydrophobic  
sequence at positions 115-121 is deleted or replaced by a  
hydrophilic sequence, and at least one of Trp-8, Ile-15  
and Met-42 is replaced with a hydrophilic amino acid or  
Thr-58 is replaced by Asn. The 115-121 sequence may  
be replaced by the C-terminal peptide of %%%HCG%%%.  
Also claimed are: (A) a DNA sequence encoding the  
modified %%%LH%%% beta subunit; (B) an expression  
system expressing the DNA and recombinant host cells  
containing the expression system; (C) human %%%LH%%%  
dimer containing the modified beta subunit; (D) an  
extended human %%%FSH%%% subunit in which the  
protein sequence of the C-terminal peptide represents  
positions 112-118 to 145 of %%%HCG%%% beta subunit;  
(E) recombinant DNA sequence, expression system and  
host cell; and (F) a modified human glycoprotein hormone  
selected from %%%FSH%%%, %%%LH%%%,  
%%HCG%% and thyrotropin in which the alpha subunit is  
a mutein. The modified hormones have a prolonged half-life.  
(65pp)  
? s hormone()receptor()complex

775094 HORMONE  
1146311 RECEPTOR  
1230151 COMPLEX  
S11 577 HORMONE()RECEPTOR()COMPLEX  
? s s11 and fusion or chimeric

577 S11  
270152 FUSION  
38452 CHIMERIC  
S12 38455 S11 AND FUSION OR CHIMERIC  
? s s11 and (fusion or chimeric)

577 S11  
270152 FUSION  
38452 CHIMERIC  
S13 19 S11 AND (FUSION OR CHIMERIC)  
? r

>>>Unrecognizable Command  
? rd

>>>Duplicate detection is not supported for File 348.

>>>Records from unsupported files will be retained in the RD  
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S14 18 RD (unique items)  
? t s14/3,ab/all

>>>No matching display code(s) found in file(s): 399

14/3,AB/1 (Item 1 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
(c) 1998 BIOSIS. All rts. reserv.

11821551 BIOSIS Number: 98421551

Detailed analysis of the IL-5-IL-5R-alpha interaction:  
Characterization of crucial residues on the ligand and the receptor

Cornelis S; Plaetinck G; Devos R; Van Der Heyden J;  
Tavernier J; Sanderson C J; Guisez Y; Fiers W  
Roche Res. Gent, Jozef Plateaustaat 22, 9000 Ghent,  
Belgium EMBO (European Molecular Biology Organization)  
Journal 14 (14). 1995. 3395-3402.

Full Journal Title: EMBO (European Molecular Biology  
Organization) Journal

ISSN: 0261-4189

Language: ENGLISH

Print Number: Biological Abstracts Vol. 100 Iss. 007 Ref.  
099143 The receptor for interleukin-5 (IL-5) is composed  
of two different subunits. The IL-5 receptor alpha  
(IL-5R-alpha) is required for ligand-specific binding while  
association with the beta-chain results in increased binding  
affinity. Murine IL-5 (mIL-5) has similar activity on human and  
murine cells, whereas human IL-5 (hIL-5) has marginal activity  
on murine cells. We found that the combined substitution of  
K84 and N108 on hIL-5 by their respective murine counterpart  
yields a molecule which is as potent as mIL-5 for growth  
stimulation of a murine cell line. Since the unidirectional  
species specificity is due only to the interaction with the  
IL-5R-alpha subunit, we have used %%%chimeric%%%  
IL-5R-alpha molecules to define regions of hIL-5R-alpha  
involved in species-specific hIL-5 ligand binding. We found  
that this property is largely determined by the  
NH-2-terminal module of hIL-5R-alpha, and detailed analysis  
defined D56 and to a lesser extent E58 as important for  
binding. Moreover, two additional residues, D55 and Y57,  
were identified by alanine scanning mutagenesis within the  
same region. Based on the observed homology between  
the NH-2-terminal module and the membrane proximal  
(WSXWS-containing) module of hIL-5R-alpha we located this  
stretch of four amino acid residues (D55, D56, Y57 and E58)  
in the loop region that connects the C and D beta-strands on  
the proposed tertiary structure of the NH-2-terminal module.  
Finally, by comparison with residues involved in ligand  
binding on the elucidated structure of the growth  
hormone-growth %%%hormone%%% %%%receptor%%%  
%%%complex%%%, residue R188 on hIL-5R-alpha was  
identified as contributing to ligand interaction.

14/3,AB/2 (Item 1 from file: 156)  
DIALOG(R)File 156:Toxline(R)  
(c) format only 1998 The Dialog Corporation. All rts. reserv.  
02470939 Subfile: TOXBIB-95-015035

Amino acid substitutions in the hormone-binding domain  
of the human androgen receptor alter the stability of the  
%%%hormone%%% %%%receptor%%%  
%%%complex%%%.

Marcelli M; Zoppi S; Wilson CM; Griffin JE; McPhaul MJ  
Department of Internal Medicine, University of Texas  
Southwestern Medical Center at Dallas 75235-8857.

Source: J Clin Invest; VOL 94, ISS 4, 1994, P1642-50 ISSN:  
0021-9738 Coden: HS7

Language: ENGLISH

Document Type: JOURNAL ARTICLE

We have investigated the basis of androgen resistance in  
seven unrelated individuals with complete testicular

feminization or Reifenstein syndrome caused by single amino  
acid substitutions in the hormone-binding domain of the  
androgen receptor. Monolayer-binding assays of cultured  
genital skin fibroblasts demonstrated absent ligand binding,  
qualitative abnormalities of androgen binding, or a  
decreased amount of qualitatively normal receptor. The  
consequences of these mutations were examined by  
introducing the mutations by site-directed mutagenesis into the  
androgen receptor cDNA sequence and expressing the mutant  
cDNAs in mammalian cells. The effects of the amino acid  
substitutions on the binding of different androgens and on the  
capacity of the ligand-bound receptors to activate a reporter  
gene were investigated. Substantial differences were found in  
the responses of the mutant androgen receptors to  
incubation with testosterone, 5 alpha-dihydrotestosterone,  
and mibolerone. In several instances, increased doses of  
hormone or increased frequency of hormone addition to  
the incubation medium resulted in normal or near normal  
activation of a reporter gene by cells expressing the mutant  
androgen receptors. These studies suggest that the stability  
of the %%%hormone%%% %%%receptor%%%  
%%%complex%%% is a major determinant of receptor  
function in vivo.

14/3,AB/3 (Item 2 from file: 156)

DIALOG(R)File 156:Toxline(R)

(c) format only 1998 The Dialog Corporation. All rts. reserv.  
01961006 Subfile: TOXBIB-94-158900

Identification of charged residues in an N-terminal portion  
of the hormone-binding domain of the human estrogen  
receptor important in transcriptional activity of the receptor.

Pakdel F; Reese JC; Katzenellenbogen BS

Department of Physiology and Biophysics, University of  
Illinois, Urbana 61801.

Source: Mol Endocrinol; VOL 7, ISS 11, 1993, P1408-17  
ISSN: 0888-8809 Coden: NGZ

Language: ENGLISH

Document Type: JOURNAL ARTICLE

We have shown that charged amino acids near C530 of the  
human estrogen receptor (ER) are involved in receptor  
discrimination between estrogen and antiestrogen. We now  
examine the role of charged residues, adjacent to the three  
other cysteines (381, 417, and 447) in the hormone-binding  
domain of the human ER, in the hormone-binding,  
DNA-binding, and transcription activation abilities of the  
receptor. Mutation of the one charged amino acid nearest to  
C381 gave a mutant receptor (E380Q) requiring two to three  
times less estradiol (E2) than wild type (WT) ER to  
achieve maximal activity and having activity in the absence  
of added estrogen that was 6-fold higher than that of WT  
receptor. The enhanced ability of this mutant to bind to  
estrogen response element DNA in the absence and presence  
of estrogen may, at least in part, explain its elevated,  
seemingly constitutive trans-activation activity and its  
increased sensitivity to estrogen. While more sensitive to E2,  
this E380Q mutant was less sensitive than WT ER to  
antiestrogen for suppression of transcriptional activity. Mutation  
of all three charged residues nearest to C381 (the triple mutant  
D374N, E380Q, and E385Q) resulted in a greatly reduced  
potency of the receptor in trans-activation with no change in  
estrogen-binding affinity. When K449 (near C447), highly  
conserved among steroid receptors, was mutated to Q,  
400-fold more E2 was required for maximal reporter gene  
trans-activation due to an unstable, temperature-sensitive  
%%%hormone%%%-%%%receptor%%%  
%%%complex%%%. In contrast, the mutant K416Q (near  
C417) was unaltered in E2-binding or receptor transcriptional  
activity. These studies reveal a region in the N-terminal  
portion of the hormone-binding domain (ca. amino acids

374-385) where alterations in charged residues result in either increases or decreases in receptor transcriptional activity with no change in receptor affinity for hormone. Our findings suggest that this region may be important in DNA binding and protein-protein interactions that modulate transcriptional activity of the ER. In addition, the region near C447, which is well conserved among steroid receptors, appears to be important in maintaining the receptor in a conformation that is stable at physiological (37 C) temperatures. To our knowledge, this is the first report of an ER (E380Q) with a sensitivity to E2 for trans-activation greater than that of WT receptor and having high trans-activation activity in the absence of added hormone.

14/3,AB/4 (Item 1 from file: 348)  
DIALOG(R)File 348:EUROPEAN PATENTS  
(c) 1998 EUROPEAN PATENT OFFICE. All rts. reserv.

00871466  
ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 Estrogen receptor  
Ostrogen-Rezeptor  
Recepteur d'oestrogene  
PATENT ASSIGNEE:  
Akzo Nobel N.V., (200754), Velperweg 76, 6824 BM  
Arnhem, (NL), (applicant designated states:

AT;BE;CH;DE;DK;ES;FI;FR;GB;GR;IE;IT;LI;LU;MC;NL;PT;S  
E) INVENTOR:

Mosselman, Sietse, De Edelenburg 34, 5346 VM OSS, (NL)  
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LEGAL REPRESENTATIVE:

Ogilvie-Emanuelson, Claudia Maria et al (80441), Patent  
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PATENT (CC, No, Kind, Date): EP 798378 A2 971001  
(Basic) EP 798378 A3 971229  
APPLICATION (CC, No, Date): EP 97200903 970325;  
PRIORITY (CC, No, Date): EP 96203284 961122; EP  
96200820 960326 DESIGNATED STATES: AT; BE; CH; DE;  
DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE  
INTERNATIONAL PATENT CLASS: C12N-015/12;  
C12N-015/62; C12N-015/85; C07K-014/72; C12N-001/21;  
C12N-005/16; C12Q-001/00; C12Q-001/68;  
ABSTRACT EP 798378 A2

The present invention relates to isolated DNA encoding  
novel estrogen receptors, the proteins encoded by said DNA,  
%%chimeric%% receptors comprising parts of said novel  
receptors and uses thereof. ABSTRACT WORD COUNT: 29

LANGUAGE (Publication,Procedural,Application): English;  
English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS A (English) 9709W4 548

SPEC A (English) 9709W4 7171

Total word count - document A 7719

Total word count - document B 0

Total word count - documents A + B 7719

14/3,AB/5 (Item 2 from file: 348)  
DIALOG(R)File 348:EUROPEAN PATENTS  
(c) 1998 EUROPEAN PATENT OFFICE. All rts. reserv.

00809770  
ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 Expression vectors that produce steroid  
receptors, steroid receptor chimera, screening assays for

steroid receptors and clinical assays using synthesized  
recept

Expressionsvektoren die Steroidrezeptoren produzieren,  
Steroidrezeptoren-Chimären, Screeningtests für  
Steroidrezeptoren und Verwendung der so hergestellten  
Reze

Vecteurs d'expression pour la production de récepteurs  
stéroïdes, chimeres de ces récepteurs, tests de  
dépistage pour ces récepteurs et tests cliniques utilisant  
PATENT ASSIGNEE:

BAYLOR COLLEGE OF MEDICINE, (401891), One Baylor  
Plaza, Houston, TX 77030, (US), (applicant designated  
states:

AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;NL;SE)

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(GB)

PATENT (CC, No, Kind, Date): EP 752477 A2 970108  
(Basic) EP 752477 A3 970514

APPLICATION (CC, No, Date): EP 96110474 910115;  
PRIORITY (CC, No, Date): US 464837 900116; US 639506  
910109 DESIGNATED STATES: AT; BE; CH; DE; DK; ES;  
FR; GB; IT; LI; NL; SE INTERNATIONAL PATENT CLASS:  
C12Q-001/68;

ABSTRACT EP 752477 A2

The present invention relates to a method for making an  
expression vector which produces a biological active receptor.  
The method includes synthesizing a linker having the carboxyl  
six amino acids of ubiquitin and an internal restriction site and  
cloning the synthesized linker to form a plasmid. The plasmid  
is then digested with a restriction endonuclease which is  
compatible with the internal restriction site in the synthesized  
linker. After the digestion of the plasmid a cDNA coding for  
the receptor is inserted into the compatible restriction site and  
the plasmid is then used to transform yeast. In the procedure,  
the yeast that is usually used is from the strains of  
Saccharomyces and Aspergillus. In addition, numerous vectors  
which express the human vitamin D receptor, human  
androgen receptor, human progesterone receptor, thyroid  
receptor, retinoic acid receptor, chicken progesterone  
receptor, chicken vitamin D receptor, rat vitamin D receptor  
and COUP protein are described. A further aspect of the  
invention is the reporter vector which includes the proximal  
promoter element of the yeast iso-1-cytochrome C and a  
structural gene selected from E. coli either the o-Galactosidase  
gene or the Galactokinase gene. The reporter vector is used  
to detect for agonist and antagonists for the steroid hormone  
receptor. A further element of the invention is a chimera made  
up of the DNA binding domain from one receptor and the  
hormone binding domain from another receptor. The chimera  
is used in an assay to identify the function of the unknown  
receptor component. Additional aspects are clinical and  
laboratory assays for biological compounds using the  
receptors synthesized from the expression vectors and using  
receptor vectors.

ABSTRACT WORD COUNT: 269

LANGUAGE (Publication,Procedural,Application): English;  
English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS A (English) EPAB97 1033

SPEC A (English) EPAB97 8829

Total word count - document A 9862  
Total word count - document B 0  
Total word count - documents A + B 9862

14/3,AB/6 (Item 3 from file: 348)  
DIALOG(R)File 348:EUROPEAN PATENTS  
(c) 1998 EUROPEAN PATENT OFFICE. All rts. reserv.

00785892  
ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 Hormone receptor compositions and  
methods  
Hormon-Rezeptorverbindungen und Methoden  
Compositions receptrices d'hormones et procedes  
PATENT ASSIGNEE:

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES,  
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AT;BE;CH;DE;FR;GB;IT;LI;LU;NL;SE)  
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81925 Munchen, (DE) PATENT (CC, No, Kind, Date): EP  
733705 A1 960925 (Basic) APPLICATION (CC, No, Date):  
EP 95120305 871023;

PRIORITY (CC, No, Date): US 922585 861024; US 108471  
871020 DESIGNATED STATES: AT; BE; CH; DE; FR; GB;  
IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS:  
C12N-015/12; C07K-014/72; C12N-015/70; C12N-001/21;  
C12N-005/10; C12Q-001/68;

ABSTRACT EP 733705 A1

Substantially pure DNA and plasmids containing the DNA  
which is comprised of sequences which encode proteins  
having hormone-binding and/or transcription-activating  
characteristics of a thyroid hormone. The invention further  
provides receptor proteins and modified functional forms for  
producing desired proteins in genetically engineered cells.  
One method involves inducing transcription of a gene whose  
transcription is activated by hormones complexed with  
receptors; the second is a method for engineering a cell and  
increasing and controlling production of a protein encoded by  
a gene whose transcription is activated by hormones  
complexed with receptor proteins.

ABSTRACT WORD COUNT: 109

LANGUAGE (Publication,Procedural,Application): English;  
English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS A (English) EPAB96 828

SPEC A (English) EPAB96 42784

Total word count - document A 43612

Total word count - document B 0

Total word count - documents A + B 43612

14/3,AB/7 (Item 4 from file: 348)  
DIALOG(R)File 348:EUROPEAN PATENTS  
(c) 1998 EUROPEAN PATENT OFFICE. All rts. reserv.

00632922

ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 Glycoprotein hormone receptor molecules.  
Glykoprotein-Hormonrezeptor-Molekule.  
Molecules receptrices d'hormone de glycoproteine.

PATENT ASSIGNEE:

GENENTECH, INC., (210480), 460 Point San Bruno  
Boulevard, South San Francisco California 94080, (US),  
(applicant designated states:

AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;LU;NL;SE)

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Segaloff, Deborah L., 28 Hunters Court, Iowa City Iowa  
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Armitage, Ian Michael et al (27761), MEWBURN ELLIS York  
House 23 Kingsway, London WC2B 6HP, (GB)

PATENT (CC, No, Kind, Date): EP 614975 A1 940914

(Basic) APPLICATION (CC, No, Date): EP 94104166  
900504;

PRIORITY (CC, No, Date): US 347683 890505

DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB;

IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS:

C12N-015/12; C12N-001/21; C12N-005/10; C07K-013/00;

ABSTRACT EP 614975 A1

The invention relates to the purification, and cloning of  
receptors for the luteinizing hormone, choriongonadotropin,  
follicle stimulating hormone, and thyroid stimulating hormone.  
The invention additionally concerns the uses for such  
molecules in the diagnosis and therapy of human conditions.  
ABSTRACT WORD COUNT: 41

LANGUAGE (Publication,Procedural,Application): English;  
English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS A (English) EPABF2 407

SPEC A (English) EPABF2 25992

Total word count - document A 26399

Total word count - document B 0

Total word count - documents A + B 26399

14/3,AB/8 (Item 5 from file: 348)  
DIALOG(R)File 348:EUROPEAN PATENTS  
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00479675

ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 Expression vectors that produce steroid  
receptors, steroid receptor chimera, screening assays for  
steroid receptors and clinical assays using synthesized  
recept

Expressionsvektoren die Steroidrezeptoren produzieren,  
Steroidrezeptoren-Chimären, Screeningtests für  
Steroidrezeptoren und Verwendung der so hergestellten  
Reze

Vecteurs d'expression pour la production de recepteurs  
steroides, chimeres de ces recepteurs, tests de  
depistage pour ces recepteurs et tests cliniques utilisent  
PATENT ASSIGNEE:

BAYLOR COLLEGE OF MEDICINE, (401891), One Baylor  
Plaza, Houston, TX 77030, (US), (applicant designated

states:

AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;NL;SE)

INVENTOR:

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O'Malley, Bert W., 629 Ramblewood, Houston, Texas 77079, (US) Conneely, Orla M., 7350 Kirby Drive 17, Houston, Texas 77030, (US) LEGAL REPRESENTATIVE:

Adams, William Gordon et al (27554), RAWORTH, MOSS & COOK 36 Sydenham Road, Croydon Surrey CR0 2EF, (GB) PATENT (CC, No, Kind, Date): EP 441483 A2 910814 (Basic) EP 441483 A3 921119

APPLICATION (CC, No, Date): EP 91300287 910115; PRIORITY (CC, No, Date): US 464837 900116; US 639506 910109 DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; NL; SE INTERNATIONAL PATENT CLASS: C12N-015/12; C12N-015/81; C12N-001/19; G01N-033/58; G01N-033/68; C12Q-001/68; C12Q-001/34; C12Q-001/48; ABSTRACT EP 441483 A2

The present invention relates to a method for making an expression vector which produces a biological active receptor. The method includes synthesizing a linker having the carboxyl six amino acids of ubiquitin and an internal restriction site and cloning the synthesized linker to form a plasmid. The plasmid is then digested with a restriction endonuclease which is compatible with the internal restriction site in the synthesized linker. After the digestion of the plasmid a cDNA coding for the receptor is inserted into the compatible restriction site and the plasmid is then used to transform yeast. In the procedure, the yeast that is usually used is from the strains of Saccharomyces and Aspergillus. In addition, numerous vectors which express the human vitamin D receptor, human androgen receptor, human progesterone receptor, thyroid receptor, retinoic acid receptor, chicken progesterone receptor, chicken vitamin D receptor, rat vitamin D receptor and COUP protein are described. A further aspect of the invention is the reporter vector which includes the proximal promoter element of the yeast iso-1-cytochrome C and a structural gene selected from E. coli either the  $\alpha$ -Galactosidase gene or the Galactokinase gene. The reporter vector is used to detect for agonist and antagonists for the steroid hormone receptor. A further element of the invention is a chimera made up of the DNA binding domain from one receptor and the hormone binding domain from another receptor. The chimera is used in an assay to identify the function of the unknown receptor component. Additional aspects are clinical and laboratory assays for biological compounds using the receptors synthesized from the expression vectors and using receptor vectors. (see image in original document) ABSTRACT WORD COUNT: 275

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS A (English) EPABF1 1436

SPEC A (English) EPABF1 8918

Total word count - document A 10354

Total word count - document B 0

Total word count - documents A + B 10354

14/3,AB/9 (Item 6 from file: 348)

DIALOG(R)File 348:EUROPEAN PATENTS

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00450316

ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 GAMMA RETINOIC ACID RECEPTOR  
GAMMA-RETINOINSURE-REZEPTOR

RECEPTEUR D'ACIDE GAMMA RETINOIQUE

PATENT ASSIGNEE:

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES, (273851), 10010 North Torrey Pines Road, La Jolla California 92037, (US), (applicant designated states:

AT;BE;CH;DE;ES;FR;GB;IT;LI;LU;NL;SE)

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Kolb, Helga, Dr. Dipl.-Chem. et al (49371), Hoffmann, Eitle & Partner, Patentanwalte, Postfach 81 04 20, 81904 Munchen, (DE)

PATENT (CC, No, Kind, Date): EP 479916 A1 920415

(Basic) EP 479916 A1 921007

EP 479916 B1 961120

WO 9015815 901227

APPLICATION (CC, No, Date): EP 90911356 900622; WO 90US3564 900622 PRIORITY (CC, No, Date): US 370407 890622

DESIGNATED STATES: AT; BE; CH; DE; ES; FR; GB; IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS:

C07K-014/705;

LANGUAGE (Publication,Procedural,Application): English;

English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS B (English) EPAB96 624

CLAIMS B (German) EPAB96 499

CLAIMS B (French) EPAB96 718

SPEC B (English) EPAB96 3778

Total word count - document A 0

Total word count - document B 5619

Total word count - documents A + B 5619

14/3,AB/10 (Item 7 from file: 348)

DIALOG(R)File 348:EUROPEAN PATENTS

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00448489

ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 GLYCOPROTEIN HORMONE  
RECEPTOR MOLECULES.

GLYKOPROTEIN-HORMONREZEPTOR-MOLEKULE.

MOLECULES RECEPTRICES D'HORMONE DE

GLYCOPROTEINE.

PATENT ASSIGNEE:

GENENTECH, INC., (210480), 460 Point San Bruno Boulevard, South San Francisco California 94080, (US), (applicant designated states:

AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;LU;NL;SE)

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Armitage, Ian Michael et al (27762), MEWBURN ELLIS York House 23 Kingsway, London WC2B 6HP, (GB)

PATENT (CC, No, Kind, Date): EP 471030 A1 920219 (Basic) EP 471030 B1 941214

WO 9013643 901115

APPLICATION (CC, No, Date): EP 90908349 900504; WO 90US2488 900504 PRIORITY (CC, No, Date): US 347683 890505

DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS: A61K-037/02;

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS B (English) EPBBF1 487

CLAIMS B (German) EPBBF1 390

CLAIMS B (French) EPBBF1 587

SPEC B (English) EPBBF1 23108

Total word count - document A 0

Total word count - document B 24572

Total word count - documents A + B 24572

14/3,AB/11 (Item 8 from file: 348)

DIALOG(R)File 348:EUROPEAN PATENTS

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00323537

ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 Retinoic acid receptor and derivatives thereof, DNA encoding either substance and use of the proteins and of the DNA

Retinoesaurerezeptor und Derivate davon, beide Substanzen codierende DNS und die Verwendung der Proteine und der DNS

Recepteur de l'acide retinoique et ses derivees, DNA codant pour ces deux substances et l'usage des proteines et des DNA

PATENT ASSIGNEE:

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Blaudin de The, Hugues, 28 rue Rambuteau, F-75003 Paris, (FR)

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Gutmann, Ernest et al (15992), Ernest Gutmann - Yves Plasseraud S.A. 3, rue Chauveau-Lagarde, 75008 Paris, (FR)

PATENT (CC, No, Kind, Date): EP 321362 A1 890621

(Basic) EP 321362 B1 960925

APPLICATION (CC, No, Date): EP 88403229 881216;

PRIORITY (CC, No, Date): US 133687 871216; US 134130

871217; US 209009 880620; US 278136 881130

DESIGNATED STATES: AT; BE; CH; DE; ES; FR; GB; GR;

IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS:

C12N-015/12; C12P-021/02; C12Q-001/68; C07K-014/00;

ABSTRACT EP 321362 A1

A previously isolated hepatitis B virus (HBV) integration in a 147 bp cellular DNA fragment linked to hepatocellular

carcinoma (HCC) was used as a probe to clone the corresponding complementary DNA from a human liver cDNA library. Nucleotide sequence analysis revealed that the overall structure of the cellular gene, which has been named hap, is similar to that of the DNA-binding hormone receptors. Six out of seven hepatoma and hepatoma-derived cell-lines express a 2.5 kb hap mRNA species which is undetectable in normal adult and fetal livers, but present in all non-hepatic tissues analyzed. Low stringency hybridization experiments revealed the existence of hap related genes in the human genome. The cloned DNA sequence is useful in the preparation of pure hap protein and as a probe in the detection and isolation of complementary DNA and RNA sequences. The hap protein is a retinoic acid (RA) receptor identified as RAR-b.

ABSTRACT WORD COUNT: 153

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS A (English) EPABF1 685

CLAIMS B (English) EPAB96 823

CLAIMS B (German) EPAB96 759

CLAIMS B (French) EPAB96 914

SPEC A (English) EPABF1 13581

SPEC B (English) EPAB96 13659

Total word count - document A 14268

Total word count - document B 16155

Total word count - documents A + B 30423

14/3,AB/12 (Item 9 from file: 348)

DIALOG(R)File 348:EUROPEAN PATENTS

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00319376

ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 Retinoic acid receptor composition and method for identifying ligands.

Retinoesaur-Rezeptor-Komposition und Verfahren zur Ligand-Identifizierung. Composition de recepteur de l'acide retinoique et procede d'identification de ligands.

PATENT ASSIGNEE:

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES, (273851), 10010 North Torrey Pines Road, La Jolla California 92037, (US), (applicant designated states:

AT;BE;CH;DE;ES;FR;GB;GR;IT;LI;LU;NL;SE)

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Ong, Estelita Sebastian,, 6307 Hannon Court, San Diego, CA

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Lane, San Diego, CA 92128, (US) Umesono, Kazuhiko,, 4178

Decoro Street, No. 60, San Diego, CA 92122, (US)

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LEGAL REPRESENTATIVE:

Kolb, Helga, Dr. Dipl.-Chem. et al (49371), Hoffmann, Eitle &

Partner, Patentanwalte, Postfach 81 04 20, D-81904

Munchen, (DE) PATENT (CC, No, Kind, Date): EP 325849

A2 890802 (Basic) EP 325849 A3

911016

EP 325849 B1 950705

APPLICATION (CC, No, Date): EP 88311477 881202;

PRIORITY (CC, No, Date): US 128331 871202; US 276536

881130 DESIGNATED STATES: AT; BE; CH; DE; ES; FR;

GB; GR; IT; LI; LU; NL; SE INTERNATIONAL PATENT

CLASS: C12N-015/12; C12P-021/02; C12N-015/62;



C12N-005/10; C12Q-001/68;

ABSTRACT EP 325849 A2

A novel retinoic acid receptor is disclosed. The novel receptor is encoded for by cDNA carried on plasmid pHRAR1, which has been deposited with the American Type Culture Collection for patent purposes. %%%Chimeric%%% receptor proteins are also disclosed. The chimera are constructed by exchanging functional domains between the glucocorticoid, the mineralocorticoid, the estrogen-related, the thyroid and the retinoic acid receptors. In addition, a novel method for identifying functional ligands for receptor proteins is disclosed. The method, which takes advantage of the modular structure of the hormone receptors and the idea that the functional domains may be interchangeable, replaces the DNA-binding domain of a putative novel receptor with the DNA-binding domain of a known receptor such as the glucocorticoid receptor. The resulting %%%chimeric%%% construction, when expressed in cells, produces a hybrid receptor whose activation of a ligand-(e.g., glucocorticoid) inducible promoter is dependent on the presence of the new ligand. The novel method is illustrated in part by showing that the ligand for the new receptor protein is the retinoid, retinoic acid.

ABSTRACT WORD COUNT: 174

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS A (English) EPABF1 1278

CLAIMS B (English) EPAB95 2782

CLAIMS B (German) EPAB95 2645

CLAIMS B (French) EPAB95 3435

SPEC A (English) EPABF1 12129

SPEC B (English) EPAB95 12247

Total word count - document A 13408

Total word count - document B 21109

Total word count - documents A + B 34517

14/3,AB/13 (Item 10 from file: 348)

DIALOG(R)File 348:EUROPEAN PATENTS

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00221880

ORDER fax of complete patent from Dialog SourceOne. See  
HELP ORDER 348 %%%Chimeric%%% plasmid vector.  
Chimarer Plasmidvektor.

Vecteur chimérique de plasmide.

PATENT ASSIGNEE:

KABUSHIKI KAISHA YAKULT HONSHA, (316160), 1-19,  
Higashishinbashi 1-chome, Minato-ku Tokyo 105, (JP),  
(applicant designated states:

AT;BE;CH;DE;FR;GB;IT;LI;LU;NL;SE)

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Tsuchida, Nobuo, 2-29-47, Kashiwa-cho Shiki, Saitama, (JP)

LEGAL REPRESENTATIVE:

Brewer, Leonard Stuart et al (42871), SANDERSON & CO.  
European Patent Attorneys 34, East Stockwell Street,  
Colchester Essex CO1 1ST, (GB) PATENT (CC, No, Kind,  
Date): EP 219214 A1 870422 (Basic) EP  
219214 B1 920408

APPLICATION (CC, No, Date): EP 86306714 860829;

PRIORITY (CC, No, Date): JP 85191427 850830

DESIGNATED STATES: AT; BE; CH; DE; FR; GB; IT; LI; LU;  
NL; SE INTERNATIONAL PATENT CLASS: C12N-015/85;

ABSTRACT EP 219214 A1

%%%Chimeric%%% plasmid vector.

A %%%chimeric%%% plasmid vector comprising first to fifth DNA fragments, wherein the first DNA fragment has a first LTR region derived from an MMTV and a 5(min)-splicing site located downstream of the first LTR region and the second DNA fragment has a 3(min)-splicing site derived from plasmid pCVSVE and located immediately downstream of the first DNA fragment, which second DNA fragment is followed by a polylinker derived from plasmid pi-AN7. The first LTR region of the first DNA fragment comprises a hormone dependent region (or a %%%hormone%%% %%%receptor%%% %%%complex%%% binding region) and an MMTV promoter region located downstream of the hormone dependent region. The third DNA fragment has a second LTR region derived from an MMN and having a transcription termination site, while the fourth DNA fragment comprises an SV40 promoter region derived from plasmid pSV2gpt and an Eco-gpt gene region derived from the plasmid pSV2gpt and operable as a gene marker. The first and fourth DNA fragments are linked together through the fifth DNA fragment which comprises an ampicillin resistance gene region derived from plasmid pBR332 and a replication origin derived from the plasmid pBR332.

ABSTRACT WORD COUNT: 191

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:

Available Text Language Update Word Count

CLAIMS B (English) EPBBF1 467

CLAIMS B (German) EPBBF1 449

CLAIMS B (French) EPBBF1 514

SPEC B (English) EPBBF1 5807

Total word count - document A 0

Total word count - document B 7237

Total word count - documents A + B 7237

14/3,AB/14 (Item 1 from file: 434)

DIALOG(R)File 434:Scisearch(R) Cited Ref Sci

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14023503 Genuine Article#: RK331 Number of References:

49 Title: CRYSTAL-STRUCTURE OF A COMPLEX  
BETWEEN INTERFERON-GAMMA AND ITS SOLUBLE  
HIGH-AFFINITY RECEPTOR

Author(s): WALTER MR; WINDSOR W; NAGABHUSHAN  
TL; LUNDELL DJ; LUNN CA; ZAUODNY PJ; NARULA SK  
Corporate Source: UNIV ALABAMA,DEPT  
PHARMACOL/BIRMINGHAM//AL/35294; UNIV  
ALABAMA,CTR MACROMOLEC

CRYSTALLOG/BIRMINGHAM//AL/35294; SCHERING  
PLOUGH CORP,RES INST/KENILWORTH//NJ/07033  
Journal: NATURE, 1995, V376, N6537 (JUL 20), P230-235  
ISSN: 0028-0836

Language: ENGLISH Document Type: ARTICLE

Abstract: The crystal structure of interferon-gamma bound to the extracellular fragment of its high-affinity cell-surface receptor reveals the first view of a class-2 cytokine receptor-ligand complex. In the complex, one interferon-gamma homodimer binds two receptor molecules. Unlike the class-1 growth %%%hormone%%% %%%receptor%%% %%%complex%%%, the two interferon-gamma receptors do not interact with one another and are separated by 27 Angstrom. Upon receptor binding, the flexible As loop of interferon-gamma undergoes a conformational change that includes the formation of a 3(10) helix.

14/3,AB/15 (Item 2 from file: 434)  
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci  
(c) 1998 Inst for Sci Info. All rts. reserv.

14000492 Genuine Article#: RG360 Number of References:  
6 Title: STRUCTURAL AND FUNCTIONAL EPITOPES IN  
THE GROWTH-%%HORMONE%%  
%%RECEPTOR%% COMPLEX%%  
Author(s): WELLS JA  
Corporate Source: GENENTECH INC,460 SAN BRUNO  
BLVD/S SAN  
FRANCISCO//CA/94080  
Journal: BIO-TECHNOLOGY, 1995, V13, N7 (JUL), P647-651  
ISSN: 0733-222X  
Language: ENGLISH Document Type: ARTICLE

14/3,AB/16 (Item 3 from file: 434)  
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci  
(c) 1998 Inst for Sci Info. All rts. reserv.

13967661 Genuine Article#: RD907 Number of References:  
12 Title: STRUCTURE OF THE GROWTH  
%%HORMONE%%-%%RECEPTOR%%  
%%COMPLEX%% AND MECHANISM OF  
RECEPTOR SIGNALING  
Author(s): KOSSIAKOFF AA  
Corporate Source: GENENTECH INC,DEPT PROT  
ENGN,460 POINT SAN BRUNO BLVD/S SAN  
FRANCISCO//CA/94080  
Journal: JOURNAL OF NUCLEAR MEDICINE, 1995, V36, N6  
(JUN), PS14-S16 ISSN: 0161-5505  
Language: ENGLISH Document Type: ARTICLE  
Abstract: The structure of the growth  
%%hormone%%-%%receptor%%  
%%complex%% discussed here is the first such system to  
be studied at the level of atomic detail and provides unique  
information that elucidates the mechanism of signal  
transduction of an important receptor family. The growth  
hormone receptor is a single-pass receptor, with an  
extracellular protein domain, a transmembrane domain and an  
intracellular protein domain. Structural data, obtained by  
crystallography, indicate that there are actually two growth  
hormone receptors that encapsulate the bound hormone.  
Although the topology of the hormone is asymmetric, the  
receptors can use their same sequence of residues to bind  
to different structural motifs by changing conformation. This  
mechanism of aggregation controls signal transduction. It  
may be possible to use this information in the design of  
radiolabeled ligands for molecular nuclear medicine studies  
involving the concentration or occupancy of growth receptors.

14/3,AB/17 (Item 4 from file: 434)  
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci  
(c) 1998 Inst for Sci Info. All rts. reserv.

13683472 Genuine Article#: QH590 Number of References:  
32 Title: STOICHIOMETRY OF THE ATRIAL NATRIURETIC  
FACTOR-R1 RECEPTOR COMPLEX IN THE BOVINE  
ZONA GLOMERULOSA  
Author(s): RONDEAU JJ; MCNICOLL N; GAGNON J;  
BOUCHARD N; ONG H; DELEAN A Corporate Source: UNIV  
MONTREAL,DEPT PHARMACOL/MONTREAL/PQ H3C  
3J7/CANADA/; UNIV MONTREAL,DEPT  
PHARMACOL/MONTREAL/PQ H3C 3J7/CANADA/; UNIV  
MONTREAL,FAC PHARM/MONTREAL/PQ H3C  
3J7/CANADA/; CEA/GRENOBLE//FRANCE/; CNRS,URA  
1333/GRENOBLE//FRANCE/  
Journal: BIOCHEMISTRY, 1995, V34, N7 (FEB 21),

P2130-2136  
ISSN: 0006-2960  
Language: ENGLISH Document Type: ARTICLE  
Abstract: The atrial natriuretic R1 receptor is a membrane  
protein that is present as an apparently preassociated  
noncovalent oligomer in the absence of ligand as suggested  
by steric exclusion studies and cross-linking experiments in  
physiological and recombinant receptor expression systems.  
The association state of this receptor oligomer was studied  
in the presence of amiloride and ATP, two known modulators of  
the R1 receptor functions with both the intact receptor and a  
cytoplasmic domain-deleted form obtained by limited  
proteolysis with trypsin. It was shown by steric exclusion on  
Superose 6 column that amiloride increased the affinity of  
ANF for the native and truncated receptor, in contrast with  
ATP, whose destabilizing effect on ANF binding was  
abolished by truncation of the cytoplasmic domain. Neither  
amiloride nor ATP exerts its effects by altering the aggregation  
state of the receptor. Comparison of the measured number  
of ANF binding sites with immunoassayable receptor protein  
revealed that the stoichiometry of ANF binding to the R1  
receptor was 1:2. This was confirmed by using an ANF  
analog that bears a photoactivatable group at both of its ends,  
showing that ANF, as for the growth  
%%hormone%%-%%receptor%%  
%%complex%%, interacts with both the receptor subunits  
and specifically cross-links a dimeric form of the receptor.  
The potential pharmacological consequences of this 1:2  
stoichiometric ratio of the ANF-receptor complex are  
discussed.

14/3,AB/18 (Item 5 from file: 434)  
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci  
(c) 1998 Inst for Sci Info. All rts. reserv.

11237785 Genuine Article#: GT377 Number of References:  
36 Title: CHROMATIN STRUCTURE OF  
HORMONO-DEPENDENT PROMOTERS  
Author(s): ADOM J; CARR KD; GOUILLEUX F; MARSAUD  
V; RICHARDFOX H Corporate Source: HOP KREMLIN  
BICETRE,INSERM,U33,UNITE RECH COMMUN  
HORMONALES,78 AVE GEN LECLERC/F-94275 LE  
KREMLIN BICETR//FRANCE/; HOP KREMLIN  
BICETRE,INSERM,U33,UNITE RECH COMMUN  
HORMONALES,78 AVE GEN LECLERC/F-94275 LE  
KREMLIN BICETR//FRANCE/  
Journal: JOURNAL OF STEROID BIOCHEMISTRY AND  
MOLECULAR BIOLOGY, 1991, V40, N1-3, P325-332  
Language: ENGLISH Document Type: ARTICLE  
Abstract: Transient transfections of mutated MMTV LTRs,  
driving the luciferase reporter gene, have shown the  
presence of at least one cis-acting element cooperating with  
the GREs. Studies of the chromatin structure of two  
glucocorticoid-regulated promoters, the mouse mammary  
tumor virus (MMTV) long terminal repeat (LTR), a retroviral  
promoter, and the rat tyrosine aminotransferase (TAT)  
promoter, demonstrate that both DNAs are organized into  
precisely positioned nucleosomes. Hormonal activation of  
transcription is accompanied by structural changes of one  
(MMTV LTR) or two (TAT promoter) nucleosomes associated  
with the hormone-response elements (HREs). These changes  
can be visualized by the appearance of DNaseI  
hypersensitive sites. Association of the  
%%hormone%%-%%receptor%%  
%%complex%% with the nucleus is necessary to induce  
the DNaseI hypersensitive site and to maintain transcription,  
but is not necessary to maintain DNaseI hypersensitivity.  
Anti-hormones, even when able to promote a strong binding

of the receptor to the nucleus, are unable to induce the chromatin structural change. Using cell lines containing approx. 200 copies of a MMTV LTR/(H)v-ras %%%chimeric%%% construct, we have demonstrated a strong, hormono-independent nuclear matrix interaction of sequences located just upstream and downstream of the ras coding sequences.

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 OneSearch, 6 files, 0.150 Hrs FileOS  
 \$102.60 Estimated cost this search  
 \$104.10 Estimated total session cost 0.206 Hrs.

File 155: MEDLINE(R) 1966-1998/Jun W4  
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Set Items Description

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E10	26	AU=WU CP
E11	6	AU=WU CQ
E12	18	AU=WU CR

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? e back

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E2	4		BACJK
E3	39045	3	*BACK
E4	6		BACK --ABNORMALITIES --AB
E5	2		BACK --ANALYSIS --AN
E6	52		BACK --ANATOMY AND HISTOLOGY --AH
E7	15		BACK --BLOOD SUPPLY --BS
E8	1		BACK --CYTOLOGY --CY
E9	2		BACK --DRUG EFFECTS --DE
E10	2		BACK --GROWTH AND DEVELOPMENT --GD
E11	432		BACK --INJURIES --IN
E12	24		BACK --INNERVATION --IR

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E7	363	AU=WU CC
E8	18	AU=WU CD
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E10	99	AU=WU CF
E11	11	AU=WU CG
E12	310	AU=WU CH

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 13 AU=WU CB

S1 274 E3, E6

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E7	2	AU=NARAYAN PV
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E9	3	AU=NARAYAN RA
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E11	1	AU=NARAYAN RKJ
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S2 141 E3-E7

? s s1 and s2

274 S1  
141 S2  
S3 3 S1 AND S2  
? t s3/3,ab/all

3/3,AB/1  
DIALOG(R)File 155:MEDLINE(R)  
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08970919 97179056

hCG-receptor binding and transmembrane signaling.  
Puett D; Bhowmick N; Fernandez LM; Huang J; %%%Wu C%%%; %%%Narayan P%%%; Department of Biochemistry and Molecular Biology, University of Georgia, Athens 30602, USA. puett@bchiris.biochem.uga.edu  
Mol Cell Endocrinol (IRELAND) Dec 20 1996, 125 (1-2) p55-64, ISSN 0303-7207 Journal Code: E69  
Contract/Grant No.: DK33973, DK, NIDDK  
Languages: ENGLISH  
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL The technique of site-directed mutagenesis has proven to be quite powerful in elucidating contact sites involved in the interaction of the heterodimeric glycoprotein hormones and their respective seven transmembrane (TM) G protein-coupled receptors. Our laboratory has focused on identification of the minimum core sequences of the alpha and beta subunits required for bioactivity, the minimum length of a conjoined (yoked) single-chain hCG, the amino acid residues on hCG and the LH/CG-receptor (LH/CG-R) responsible for high-affinity binding, and the regions of the receptor that are involved in TM signaling. A number of amino acid residues have been mapped on the alpha and beta subunits of hCG that appear important in receptor binding. When projected onto the crystal structure of HF-treated hCG, these residues, by and large, cluster on one side of the molecule and cover a sizeable surface area, indicating that the hormone-receptor binding interface is rather extensive. Based on mutagenesis studies of several conserved ionizable amino acid residues in the extracellular domain (ECD) of LH/CG-R and a model that we, in collaboration with Drs Laphorn and Isaacs, have developed for this region based on the crystal structure of porcine ribonuclease inhibitor, a charged region that appears to play an important role in hormone-receptor recognition has been identified. We have also delineated several regions of LH/CG-R that do not appear to participate in hCG binding but are involved in hCG-mediated signaling. These regions are located in the ECD and extracellular loop III just prior to entry into the membrane via TM helices I and VII, respectively, and in TM helices VI and VII. Similarly, a homologous region in the ECD of the FSH receptor, located with ten residues of TM helix I, is important in signaling but not hormone binding. These results suggest that ligand binding and ligand-mediated receptor activation are quasi-distinct, albeit sequential phenomena. Collectively, our mutagenesis and modeling studies, coupled with results from other laboratories, argue for a ligand-induced conformational change of the receptor that may involve a relative reorientation of the TM helices.

3/3,AB/2  
DIALOG(R)File 155:MEDLINE(R)  
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08830541 97094949

Protein engineering of a novel constitutively active hormone-receptor complex.  
%%Wu C%%%; %%%Narayan P%%%; Puett D  
Department of Biochemistry and Molecular Biology,

University of Georgia, Athens, Georgia 30602-7229, USA.  
J Biol Chem (UNITED STATES) Dec 6 1996, 271 (49) p31638-42, ISSN 0021-9258 Journal Code: HIV  
Contract/Grant No.: DK-33973, DK, NIDDK  
Languages: ENGLISH  
Document type: JOURNAL ARTICLE

Human chorionic gonadotropin (hCG) is a heterodimeric glycoprotein hormone consisting of an alpha and a beta subunit that stimulates intracellular levels of cAMP via a G protein-coupled receptor. Herein we report the engineering and characterization of a novel molecule in which the receptor and its heterodimeric ligand were covalently linked in a single polypeptide chain. The hormone-receptor complex was expressed in cells transfected with this construct, but the cells were unable to bind significant amounts of exogenous hCG. However, cleavage of the hormone with a site-specific protease rendered the receptor accessible to exogenously added hormone. Cells transfected with the hCG-receptor construct contained elevated basal levels of cAMP; moreover, addition of hormone had no significant effect. These results are consistent with a strong and stable interaction between the single-chain hormone and its covalently linked receptor that results in a constitutively active complex.

3/3,AB/3  
DIALOG(R)File 155:MEDLINE(R)  
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08568392 96192928

Functional expression of yoked human chorionic gonadotropin in baculovirus-infected insect cells.  
%%Narayan P%%%; %%%Wu C%%%; Puett D  
Department of Biochemistry and Molecular Biology, University of Georgia, Athens 30602, USA.  
Mol Endocrinol (UNITED STATES) Dec 1995, 9 (12) p1720-6, ISSN 0888-8809 Journal Code: NGZ  
Contract/Grant No.: DK-33973, DK, NIDDK  
Languages: ENGLISH  
Document type: JOURNAL ARTICLE  
hCG is a glycoprotein hormone composed of an alpha-subunit, common to all gonadotropins and to TSH, and a hormone-specific beta-subunit. The non-covalent association of the two subunits is an obligatory step for the formation of biologically active hormones. The correct assembly of the heterodimer is also important for efficient secretion of the hormone, receptor binding, and signal transduction. Herein, we have demonstrated that expression of the two subunits from independent promoters present in a single recombinant baculovirus resulted in subunit association and secretion of biologically active holoprotein by the insect cells. To determine whether the active conformation of heterodimer could be achieved when the two subunits were synthesized in tandem on a single polypeptide chain, two single chain or yoked hCG1, the C-terminus of the complete beta-subunit (145 amino acid residues) was conjoined to the N-terminus of the alpha-subunit. Yoked hCG2 was similar, except that it contained the N-terminal 123 amino acid residues of the beta-subunit. Both yoked hCG molecules bound LH/CG receptor with high affinity and stimulated adenylate cyclase and progesterone levels in transformed mouse Leydig (MA-10) cells. Therefore, the alpha- and beta-subunits are able to fold into a biologically active conformation when covalently linked. Interestingly, when compared with urinary hCG, the hormone expressed in baculovirus-infected insect cells binds to the LH/CG receptor with higher affinity, but exhibits diminished signaling, thus providing another example of a partial

dissociation between receptor binding and activation. ? e  
au=campbell r

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S5 84 E3,E4

? e au=chappel s

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38 AU=CHAPPEL SC

S6 48 E3,E4

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S5	84	E3,E4
S6	48	E3,E4
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	84	S5
	48	S6
S7	387	S4 OR S5 OR S6
? s s7 and hybrid		

387 S7

30324 HYBRID

S8 3 S7 AND HYBRID

? t s8/3,ab/all

8/3,AB/1

DIALOG(R)File 155:MEDLINE(R)

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07686867 94068417

Production and fluorescence-activated cell sorting of Escherichia coli expressing a functional antibody fragment on the external surface. Francisco JA; %%%Campbell R%%%; Iverson BL; Georgiou G

Department of Chemical Engineering, University of Texas, Austin 78712. Proc Natl Acad Sci U S A (UNITED STATES) Nov 15 1993, 90 (22) p10444-8, ISSN 0027-8424 Journal Code: PV3

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We have expressed a single chain Fv (scFv) antibody fragment, consisting of the variable heavy and variable light domains from two separate anti-digoxin monoclonal antibodies, on the external surface of Escherichia coli by fusing it to an Lpp-OmpA %%%hybrid%%% previously shown to direct heterologous proteins to the cell surface. This scFv fusion was expressed at a high level and was shown to bind the hapten with high affinity and specificity. Whole cell ELISAs, fluorescence microscopy, protease sensitivity, and flow cytometry all confirmed that the scFv was anchored on the outer membrane and was accessible on the surface.

Utilizing fluorescence-activated cell sorting, we were able to specifically enrich scFv-producing cells from a 10(5)-fold excess of control cells in only two steps. The expression of antibody fragments on the surface of E. coli is being evaluated as an attractive method for the in vitro production and selection of useful antibody fragments.

8/3,AB/2  
DIALOG(R)File 155:MEDLINE(R)  
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03857450 82215176

Effects of immunoglobulin structure on Fc receptor binding: a mouse myeloma variant immunoglobulin with a gamma 2b-gamma 2a %%%hybrid%%% heavy chain having a complete gamma 2a Fc region fails to bind to gamma 2a Fc receptors on mouse macrophages.

Birshtein BK; %%%Campbell R%%%; Diamond B  
J Immunol (UNITED STATES) Aug 1982, 129 (2) p610-4,  
ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: AI 12509, AI, NIAID; AI 10702, AI,  
NIAID; 16166 Languages: ENGLISH

Document type: JOURNAL ARTICLE

We report here the primary structure of an immunoglobulin heavy chain synthesized by ICR 16, a variant of the MPC 11 mouse myeloma cell line. The ICR 16 heavy chain is a gamma 2b-gamma 2a %%%hybrid%%%, consisting of the CH1 domain of gamma 2b and the hinge, CH2 and CH3 domains of gamma 2a subclasses. The genetic mechanism by which ICR 16 occurred may be recombination, based on homologies in both coding and intervening sequences in gamma 2b and gamma 2a constant region genes. Although the Fc fragment of ICR 16 is completely gamma 2a-like and has been shown to bind to gamma 2a Fc receptors on mouse macrophages, the intact H2L2 molecules is unable to do so. Such an observation underscores the crucial role that conformation may play in the ability of immunoglobulins to carry out biologic functions.

8/3,AB/3  
DIALOG(R)File 155:MEDLINE(R)  
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03823618 80198307

A gamma 2b-gamma 2a %%%hybrid%%% immunoglobulin heavy chain produced by a variant of the MPC 11 mouse myeloma cell line.

Birshtein BK; %%%Campbell R%%%; Greenberg ML  
Biochemistry (UNITED STATES) Apr 29 1980, 19 (9)  
p1730-7, ISSN 0006-2960 Journal Code: A0G

Languages: ENGLISH

Document type: JOURNAL ARTICLE

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Set	Items	Description
S1	274	E3, E6
S2	141	E3-E7
S3	3	S1 AND S2
S4	255	E3,E16
S5	84	E3,E4
S6	48	E3,E4
S7	387	S4 OR S5 OR S6
S8	3	S7 AND HYBRID
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? s s7 and chimera?

387 S7  
18587 CHIMER?  
S9 11 S7 AND CHIMER?  
? s s9 not s8

11 S9  
3 S8  
S10 11 S9 NOT S8  
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10/3,AB/1  
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09097760 97278315

%%Chimeric%%% proteins can exceed the sum of their parts: implications for evolution and protein design.

%%Campbell RK%%%; Bergert ER; Wang Y; Morris JC;  
Moyle WR Department of OBGYN, Robert Wood Johnson  
(Rutgers) Medical School, Piscataway, NJ 08854, USA.

Nat Biotechnol (UNITED STATES) May 1997, 15 (5)  
p439-43, ISSN 1087-0156 Journal Code: CQ3

Contract/Grant No.: HD14907, HD, NICHD; HD15454, HD,  
NICHD; DK42008, DK, NIDDK

Languages: ENGLISH

Document type: JOURNAL ARTICLE

%%Chimeric%%% analogs derived from pairs of homologous proteins routinely exhibit activities found in one or both parents. We describe %%chimeras%%% of two glycoprotein hormones, human chorionic gonadotropin (hCG) and human follitropin (hFSH), that exhibit activity unique to a third family member, human thyrotropin (hTSH). The results show that biological activity can be separated from hormone-specific amino acid residues. This is consistent with a model for the evolution of homologous ligand-receptor pairs involving gene duplication and the creation of inhibitory determinants that restrict binding. Disruption of these determinants can unmask activities characteristic of other members of a protein family. Combining portions of two ligands to create analogs with properties of a third family member can facilitate identifying key determinants of protein-protein interaction and may be a useful strategy for creating novel therapeutics. In the case of the glycoprotein hormones, this showed that two different hormone regions (i.e., the seat-belt and the intersubunit groove) appear to limit inappropriate contacts with receptors for other members of this family. These observations also have important caveats for %%chimera%%% -based protein design because an unexpected gain of function may limit the therapeutic usefulness of some %%chimeras%%%.

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08953900 97166171

Influence of subunit interactions on lutropin specificity. Implications for studies of glycoprotein hormone function.

Cosowsky L; Lin W; Han Y; Bernard MP; %%%Campbell RK%%%; Moyle WR Department of Obstetrics and Gynecology, Robert Wood Johnson (Rutgers) Medical School, Piscataway, New Jersey 08854, USA.

J Biol Chem (UNITED STATES) Feb 7 1997, 272 (6)  
p3309-14, ISSN 0021-9258 Journal Code: HIV

Contract/Grant No.: HD14907, HD, NICHD; HD15454, HD,  
NICHD Languages: ENGLISH

Document type: JOURNAL ARTICLE

Bovine lutropin (bLH) and human chorionic gonadotropin

(hCG) are heterodimeric glycoprotein hormones required for reproduction. Both bind rat LH receptors (rLHRs), but hCG binds human LH receptors (hLHRs) 1000-10,000 fold better than bLH. We tested the premise that this difference in affinity could be used to identify lutropin receptor contacts. Heterodimers containing hCG/bLH alpha- or beta-subunit %%%chimeras%%% that bound hLHR like hCG (or bLH) were expected to have hCG (or bLH) residues at the receptor contact sites. Analogs containing one subunit derived from hCG bound hLHR much more like hCG than bLH, indicating that each bLH subunit contains all the residues sufficient for high affinity hLHR binding. Indeed, the presence of bovine alpha-subunit residues increased the activities of some hCG analogs. The low hLHR activity of bLH was due primarily to an interaction between its alpha-subunit and beta-subunit residue Leu95. Leu95 does not appear to contact the hLHR since it did not influence the hLHR activity of heterodimers containing human alpha-subunit. These observations show that interactions within and between the subunits can significantly influence the activities of lutropins, thereby confounding efforts to identify ligand residues that contact these receptors.

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08616483 96281915

HLA-DR4-IE %%%chimeric%%% class II transgenic, murine class II-deficient mice are susceptible to experimental allergic encephalomyelitis. Ito K; Bian HJ; Molina M; Han J; Magram J; Saar E; Belunis C; Bolin DR; Arceo R; %%%Campbell R%%%; Falcioni F; Vidovic D; Hammer J; Nagy ZA Department of Inflammation and Autoimmune Diseases, Hoffmann-La Roche Inc., Nutley, New Jersey 07110, USA.

J Exp Med (UNITED STATES) Jun 1 1996, 183 (6) p2635-44, ISSN 0022-1007 Journal Code: I2V

Languages: ENGLISH

Document type: JOURNAL ARTICLE

To investigate the development of HLA-DR-associated autoimmune diseases, we generated transgenic (Tg) mice with HLA-DRA-IE alpha and HLA-DRB1\*0401-IE beta %%%chimeric%%% genes. The transgene-encoded proteins consisted of antigen-binding domains from HLA-DRA and HLA-DRB1\*0401 molecules and the remaining domains from the IE(d)-alpha and IE(d)-beta chains. The %%%chimeric%%% molecules showed the same antigen-binding specificity as HLA-DRB1\*0401 molecules, and were functional in presenting antigens to T cells. The Tg mice were backcrossed to MHC class II-deficient (IA beta-, IE alpha-) mice to eliminate any effect of endogenous MHC class II genes on the development of autoimmune diseases. As expected, IA alpha beta or IE alpha beta molecules were not expressed in Tg mice. Moreover, cell-surface expression of endogenous IE beta associated with HLA-DRA-IE alpha was not detectable in several Tg mouse lines by flow cytometric analysis. The HLA-DRA-IE alpha/HLA-DRB1\*0401-IE beta molecules rescued the development of CD4+ T cells in MHC class II-deficient mice, but T cells expressing V beta 5, V beta 11, and V beta 12 were specifically deleted. Tg mice were immunized with peptides, myelin basic protein (MBP) 87-106 and proteolipid protein (PLP) 175-192, that are considered to be immunodominant epitopes in HLA-DR4 individuals. PLP175-192 provoked a strong proliferative response of lymph node T cells from Tg mice, and caused inflammatory lesions in white matter of the CNS and symptoms of experimental allergic encephalomyelitis (EAE). Immunization with MBP87-106 elicited a very weak proliferative T cell

response and caused mild EAE. Non-Tg mice immunized with either PLP175-192 or MBP87-106 did not develop EAE. These results demonstrated that a human MHC class II binding site alone can confer susceptibility to an experimentally induced murine autoimmune disease.

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08386568 95378256

Model of human chorionic gonadotropin and lutropin receptor interaction that explains signal transduction of the glycoprotein hormones. Moyle WR; %%%Campbell RK%%%; Rao SN; Ayad NG; Bernard MP; Han Y; Wang Y Department of Obstetrics/Gynecology, Robert Wood Johnson (Rutgers) Medical School, Piscataway, New Jersey 08854, USA.

J Biol Chem (UNITED STATES) Aug 25 1995, 270 (34) p20020-31, ISSN 0021-9258 Journal Code: HIV

Contract/Grant No.: HD14907, HD, NICHD; HD24650, HD, NICHD; HD15454, HD, NICHD

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The goal of these studies was to devise a model that explains how human chorionic gonadotropin (hCG) interacts with lutropin (LH) receptors to elicit a hormone signal. Here we show that alpha-subunit residues near the N terminus, the exposed surface of the cysteine knot, and portions of the first and third loops most distant from the beta-subunit interface were recognized by antibodies that bound to hCG-receptor complexes. These observations were combined with similar data obtained for the beta-subunit (Cosowsky, L., Rao, S.N.V., Macdonald, G.J., Papkoff, H., Campbell, R.K., and Moyle, W.R. (1995) J. Biol. Chem. 270, 20011-20019), information on residues of hCG that can be changed without disrupting hormone function, the crystal structure of deglycosylated hCG, and the crystal structure of a leucine-repeat protein to devise a model of hCG-receptor interaction. This model suggest that the extracellular domain of the LH receptor is "U-" or "J"-shaped and makes several contacts with the transmembrane domain. High affinity hormone binding results from interactions between residues in the curved portion of the extracellular domain of the receptor and the groove in the hormone formed by the apposition of the second alpha-subunit loop and the first and third beta-subunit loops. Most of the remainder of the hormone is found in the large space between the arms of the extracellular domain and makes few, if any, additional specific contacts with the receptor needed for high affinity binding. Signal transduction is caused by steric or other influences of the hormone on the distance between the arms of the extracellular domain, an effect augmented by the oligosaccharides. Because the extracellular domain is coupled at multiple sites to the transmembrane domain, the change in conformation of the extracellular domain is relayed to the transmembrane domain and subsequently to the cytoplasmic surface of the plasma membrane. While the model does not require the hormone to contact the transmembrane domain to initiate signal transduction, small portions of both subunits may be near the transmembrane domain and assist in initiating the hormonal signal. This is the first model that is consistent with all known information on the activity of the gonadotropins including the amounts of the hormone that are exposed in the hormone-receptor complex, the apparent lack of specific contacts between much of the hormone and the receptor, and the roles of the oligosaccharides in signal transduction.(ABSTRACT TRUNCATED AT 400 WORDS)

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08386567 95378255

The groove between the alpha- and beta-subunits of hormones with lutropin (LH) activity appears to contact the LH receptor, and its conformation is changed during hormone binding.

Cosowsky L; Rao SN; Macdonald GJ; Papkoff H; %%%Campbell RK%%%; Moyle WR Department of Obstetrics/Gynecology, Robert Wood Johnson (Rutgers) Medical School, Piscataway, New Jersey 08854, USA.

J Biol Chem (UNITED STATES) Aug 25 1995, 270 (34) p20011-9, ISSN 0021-9258 Journal Code: HIV  
Contract/Grant No.: HD05722, HD, NICHD; HD14907, HD, NICHD; HD24650, HD, NICHD; +

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Gonadotropins are heterodimeric glycoprotein hormones that control vertebrate fertility through their actions on gonadal lutropin (luteinizing hormone, LH) and follitropin (follicle-stimulating hormone, FSH) receptors. The beta-subunits of these hormones control receptor binding specificity; however, the region of the beta-subunit that contacts the receptor has not been identified. By a process of elimination we show this contact to be the portions of beta-subunit loops one and three found in a hormone groove created by the juxtaposition of the alpha- and beta-subunits. Most other regions of the beta-subunit can be recognized by antibodies that bind to human chorionic hormone (hCG)-receptor complexes or replaced without disrupting hormone function. Using a series of bovine LH/hCG and human FSH/hCG beta-subunit %%%chimeras%%% we identified key hCG beta-subunit residues in the epitopes of two antibodies that bind to hCG-receptor complexes. These epitopes include the surfaces of beta-subunit loops one and three near residue 74 on the outside of the hormone groove and parts of the C-terminal end of the "seat belt" that holds the two subunits together. The antibody that recognized residue 74 bound to receptor complexes containing most mammalian lutropins better than to the free hormones, an indication that the outside surface of the beta-subunit groove is altered during hormone binding. This region of the beta-subunit is furthest from the alpha-subunit and is recognized equally well in the free beta-subunit and in the heterodimer. Thus, the receptor associated increase in antibody binding appears due to an interaction of this portion of the beta-subunit with the receptor and not to an effect of the receptor on the relative positions of the alpha- and beta-subunits. Unlike most previous studies designed to identify portions of the beta-subunit likely to contact the LH receptor, this indirect approach provides data that are more easily interpreted because it does not rely on the use of mutations that disrupt hormone function. The approach described here should be valuable for studying the receptor interactions of other complex ligands.

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08014455 95001918

High-affinity, specific factor IXa binding to platelets is mediated in part by residues 3-11.

Ahmad SS; Rawala-Sheikh R; Cheung WF; %%%Jameson BA%%%; Stafford DW; Walsh PN  
Sol Sherry Thrombosis Research Center, Department of Biochemistry, Temple University School of Medicine,

Philadelphia, Pennsylvania 19140. Biochemistry (UNITED STATES) Oct 11 1994, 33 (40) p12048-55, ISSN 0006-2960 Journal Code: A0G

Contract/Grant No.: HL45486, HL, NHLBI; HL2566, HL, NHLBI; HL46213, HL, NHLBI; +

Languages: ENGLISH

Document type: JOURNAL ARTICLE

To identify the amino acids in the Gla domain that mediate factor IXa binding to human platelets, we have used %%%chimeric%%% molecules and point mutations in the Gla domain of recombinant factor IX, based on molecular modeling using the coordinates of the Gla domain of bovine prothrombin, which reveals two surface structures whose sequences differ among factor IX, factor X, and factor VII. Binding to thrombin-activated platelets of factor IXa in the presence of factor VIIIa (2 units/mL) and factor X (1.5 microM) revealed a stoichiometry of approximately 550 sites per platelet with a Kd of approximately 0.65 nM compared with a Kd of approximately 2.5 nM in the absence of factor VIIIa and factor X. In contrast, mutations of factor IX to factor X residues at positions 4 and 5 or at positions 9, 10, and 11 results in decreases in the number of sites and affinity of factor IXa binding in the presence or absence of factor VIIIa and factor X. A %%%chimera%%% consisting of the Gla domain of factor VII with factor IX residues at positions 33, 34, 35, 39, and 40 displayed abnormal factor IXa binding and a decreased Vmax and a normal Km for factor X activation, and the replacement of amino acid residues 3-10 with those of factor IX restored normal binding and factor X activation kinetics to this %%%chimeric%%% protein.(ABSTRACT TRUNCATED AT 250 WORDS)

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07886010 94195396

Co-evolution of ligand-receptor pairs.

Moyle WR; %%%Campbell RK%%%; Myers RV; Bernard MP; Han Y; Wang X Department of Obstetrics and Gynecology, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson (Rutgers) Medical School, Piscataway 08854.

Nature (ENGLAND) Mar 17 1994, 368 (6468) p251-5, ISSN 0028-0836 Journal Code: NSC

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Specific receptors for lutropin (luteinizing hormone; LH) and follitropin (follicle-stimulating hormone; FSH) mediate the actions of human chorionic gonadotropin (hCG) and FSH5 on the gonads. Here we report that short independent sequences of the beta-subunit enable hCG to distinguish between the receptors for FSH and LH. Residues between the 11th and 12th cysteines restrict FSH receptor binding; residues between the 10th and 11th cysteines and, to a much lesser extent, residues carboxy-terminal to the 12th cysteine also affect LH receptor binding. CF101-109, an hCG analogue containing hFSH beta residues between the 11th and 12th cysteines, had high affinity for both LH and FSH receptors. Modifications to CF101-109 that reduce binding to either LH or FSH receptors yield gonadotropin analogues having differing ratios of LH:FSH activity. Ligand-binding specificity of the LH receptor is determined by residues encoded by parts of exons 2-4 and 7-9 which prevent hFSH binding but have little effect on hCG binding. FSH receptor specificity is controlled primarily by residues encoded by exons 5 and 6 that prevent hCG binding but have little effect on hFSH binding. These determinants can be interchanged to



create receptor analogues that bind hCG and hFSH. Our observations support a model in which distinct negative determinants restrict ligand-receptor interaction. This explains coevolution of binding specificity in families of homologous ligands and their receptors. Natural or designed manipulation of these determinants leads to the 'evolution' of new, specific protein-protein interactions.

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07335869 92192337

Assembly and expression of a synthetic gene encoding the bovine glycoprotein hormone alpha-subunit.  
%%Campbell RK%%; Erfle H; Barnett RW; Moyle WR  
University of Medicine and Dentistry of New Jersey, Robert Wood Johnson (Rutgers) Medical School, Piscataway 08854.  
Mol Cell Endocrinol (NETHERLANDS) Feb 1992, 83 (2-3) p195-200, ISSN 0303-7207 Journal Code: E69  
Contract/Grant No.: HD14709, HD, NICHD  
Languages: ENGLISH  
Document type: JOURNAL ARTICLE

The glycoprotein hormones are a family of alpha beta heterodimeric proteins which are responsible for gonadal and thyroid function. In previous studies we employed %%chimeric%% glycoprotein hormone beta-subunits to identify amino acid residues critical for binding to receptors and antibodies. To facilitate similar studies of the alpha-subunit of these hormones, we assembled a 406 bp synthetic gene which encodes the human alpha-subunit leader sequence and the secreted portion of the bovine alpha-subunit. It contains unique restriction sites that can be used for cassette mutagenesis or for making human/bovine alpha-subunit %%chimeras%%. The gene was assembled from eight long oligodeoxynucleotides in a single ligation and its structure verified by DNA sequencing. Co-transfection of COS-7 cells with the synthetic gene and the cDNA for human chorionic gonadotropin (hCG) beta-subunit resulted in the secretion of a functional alpha beta heterodimer which bound to luteinizing hormone receptors. The protein was recognized by several monoclonal antibodies including B109, an antibody to a conformational epitope which binds hCG but not the free bovine alpha-, human alpha-, or hCG beta-subunits. This suggests that the binding site for B109 may be formed by residues located primarily within the hCG beta-subunit and that formation of this epitope requires a change in conformation of the beta-subunit when it combines with the alpha-subunit.

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06984803 90256768

Localization of residues that confer antibody binding specificity using human chorionic gonadotropin/luteinizing hormone beta subunit %%chimeras%% and mutants.

Moyle WR; Matzuk MM; %%Campbell RK%%;  
Cogliani E; Dean-Emig DM; Krichevsky A; Barnett RW;  
Boime I

Department of Obstetrics/Gynecology, Robert Wood Johnson (Rutgers) Medical School, Piscataway, New Jersey 08854.

J Biol Chem (UNITED STATES) May 25 1990, 265 (15) p8511-8, ISSN 0021-9258 Journal Code: HIV

Contract/Grant No.: HD14907, HD, NICHD; HD23398, HD, NICHD; HD15454, HD, NICHD; +

Languages: ENGLISH  
Document type: JOURNAL ARTICLE

The glycoprotein hormones are a family of conserved heterodimeric proteins which share a common alpha subunit but differ in their hormone-specific beta subunits. We used %%chimeras%% of human chorionic gonadotropin (hCG) and luteinizing hormone (hLH) beta subunits to identify residues which enable monoclonal antibodies (mAb) to distinguish the two hormones. The LH beta-CG beta %%chimeras%% appeared to fold similar to hCG beta, since they combined with hCG alpha and, depending on their sequences, were recognized by hCG-selective mAbs. Amino acid residues Arg8-Arg10, Gly47-Ala51, and Gln89-Leu92 form a major epitope region and appear to be adjacent to each other on the surface of hCG beta. Gly47-Ala51 and Gln89-Leu92 are recognized by dimer-specific mAbs while Arg8-Arg10 is recognized by mAbs which have highest affinity for the free beta subunit. These observations suggest that the conformation of this region of the beta subunit changes when the alpha and beta subunits combine. Residues which are C-terminal of Asp112 form a second epitope domain. mAbs to the third domain distinguish hCG beta and hLH beta by the presence of Asn77 in hCG beta and can be detected after hCG binds to receptors. These findings were used to develop a model of hCG beta which predicts the locations of these residues and their positions relative to the alpha subunit and receptor interfaces.

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06787620 91126075

Conversion of human choriogonadotropin into a follitropin by protein engineering.

%%Campbell RK%%; Dean-Emig DM; Moyle WR  
Department of Obstetrics & Gynecology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway 08854.

Proc Natl Acad Sci U S A (UNITED STATES) Feb 1 1991, 88 (3) p760-4, ISSN 0027-8424 Journal Code: PV3

Contract/Grant No.: HD14709, HD, NICHD; HD24650, HD, NICHD Languages: ENGLISH

Document type: JOURNAL ARTICLE

Human reproduction is dependent upon the actions of follicle-stimulating hormone (hFSH), luteinizing hormone (hLH), and chorionic gonadotropin (hCG). While the alpha subunits of these heterodimeric proteins can be interchanged without effect on receptor-binding specificity, their beta subunits differ and direct hormone binding to either LH/CG or FSH receptors. Previous studies employing chemical modifications of the hormones, monoclonal antibodies, or synthetic peptides have implicated hCG beta-subunit residues between Cys-38 and Cys-57 and corresponding regions of hLH beta and hFSH beta in receptor recognition and activation. Since the beta subunits of hCG or hLH and hFSH exhibit very little sequence similarity in this region, we postulated that these residues might contribute to hormone specificity. To test this hypothesis we constructed %%chimeric%% hCG/hFSH beta subunits, coexpressed them with the human alpha subunit, and examined their ability to interact with LH and FSH receptors and hormone-specific monoclonal antibodies. Surprisingly, substitution of hFSH beta residues 33-52 for hCG beta residues 39-58 had no effect on receptor binding or stimulation. However, substitution of hFSH beta residues 88-108 in place of the carboxyl terminus of hCG beta

(residues 94-145) resulted in a hormone analog identical to hFSH in its ability to bind and stimulate FSH receptors. The altered binding specificity displayed by this analog is not attributable solely to the replacement of hCG beta residues 108-145 or substitution of residues in the "determinant loop" located between hCG beta residues 93 and 100.

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04889859 86159371

The lateralization of lip-read sounds: a first look.  
%%Campbell R%%  
Brain Cogn (UNITED STATES) Jan 1986, 5 (1) p1-21,  
ISSN 0278-2626 Journal Code: AM9  
Languages: ENGLISH  
Document type: JOURNAL ARTICLE  
Two tachistoscopic studies on the lateralization of lip-read still photographs in normal right handers are reported. In the first, subjects matched a still lip photograph with a heard speech sound. A clear right hemisphere (LVF) advantage emerged, despite the phonological requirements of this task. This pattern of laterality failed to interact with the type of response (same/different) or with the status of the heard phoneme; both consonant and vowel matching showed the same pattern of LVF advantage, despite the significantly greater difficulty of consonant than vowel matching in this particular task. In the second study subjects were required to speak the sound they saw being spoken by a centrally displayed face photograph. The displayed face was %%chimeric%%; that is, one side of the face was seen saying one sound, one side another. Here, a rather complex pattern of results ensued. For the speakers seen a clear expressor asymmetry emerged; speech sounds were judged more accurately when they issued from the right side of the speaker's face. However, in the LVF, and only the LFV, accuracy in reporting %%chimeric%% face sounds correlated with speed in learning to lip-read, suggesting that the LVF is systematically involved even when task demands (speaking the response, phonological analysis, small, more central displays) do not, at first sight, suggest that they should. Taken together, these studies suggest that the right hemisphere could support some aspects of the processing of seen speech in normally hearing, normally lateralized individuals. ? s s7 and fusion not (s8 or s9)

387 S7  
61744 FUSION  
3 S8  
11 S9  
S11 11 S7 AND FUSION NOT (S8 OR S9)  
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11/3,AB/1  
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08680708 96113548

Expression of *Trichoderma reesei* and *Trichoderma viride* xylanases in *Escherichia coli*.  
Sung WL; Luk CK; Chan B; Wakarchuk W; Yaguchi M;  
%%Campbell R%%; Willick G; Ishikawa K; Zahab DM  
Institute for Biological Sciences, National Research Council of Canada, Ottawa, ON, Canada.  
Biochem Cell Biol (CANADA) May-Jun 1995, 73 (5-6) p253-9, ISSN 0829-8211 Journal Code: ALR  
Languages: ENGLISH

Document type: JOURNAL ARTICLE

Synthetic genes encoding the 190 amino acid *Trichoderma reesei* xylanase II (TrX) and the closely related *Trichoderma viride* xylanases have been synthesized in a two-step procedure. Initially, a partial gene encoding amino acids 92-190 was constructed in %%fusion%% with the N-terminal half of the *Bacillus circulans* xylanase (BcX). The remaining BcX gene sequence was replaced during the assembly of the coding sequence for amino acids 1-91. Expression of the synthetic genes in *Escherichia coli* yielded recombinant xylanases with specific activity generally identical with the natural TrX. However, the recombinant TrX showed thermostability and temperature optimum lower than those of the natural TrX, thus indicating that the posttranslational modifications of the latter in its fungal host are essential to its greater stability. A mutation N19K further decreased the thermostability of the recombinant TrX.

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08578615 96212188

Thrombin-induced platelet aggregation is inhibited by the heptapeptide Leu271-Ala277 of domain 3 in the heavy chain of high molecular weight kininogen.  
Kunapuli SP; Bradford HN; %%Jameson BA%%;  
DeLa Cadena RA; Rick L; Wassell RP; Colman RW  
Sol Sherry Thrombosis Research Center, Temple University School of Medicine, Philadelphia, Pennsylvania 19140, USA.  
J Biol Chem (UNITED STATES) May 10 1996, 271 (19) p11228-35, ISSN 0021-9258 Journal Code: HIV  
Contract/Grant No.: HL45486, HL, NHLBI  
Languages: ENGLISH  
Document type: JOURNAL ARTICLE  
The ability of kininogens to modulate thrombin-induced aggregation of human platelets has been assigned to domain 3 (D3) in the common heavy chain coded for by exons 7, 8, and 9 of kininogen gene. We expressed each of the exons 7, 8, and 9, and various combinations as glutathione S-transferase %%fusion%% proteins in *Escherichia coli*. Each of the exon products 7 (Lys236-Gln292), 9 (Val293-Gly328), and 8 (Gln329-Met357), and their combinations were evaluated for the ability to inhibit thrombin induced platelet aggregation. Only products containing exon 7 inhibited platelet aggregation induced by thrombin with an IC50 of > 20 microM. A deletion mutant of exon 7 product, polypeptide 7A product (Lys236-Lys270) did not block thrombin-induced platelet aggregation, while 7B product (Thr255-Gln292) and 7C product (Leu271-Gln292) inhibited aggregation. These findings indicated that the inhibitory activity is localized to residues Leu271-Gln292. Peptides Phe279-Ile283 and Phe281-Gln292 did not block thrombin, and Asn275-Phe279 had only minimal inhibitory activity. A heptapeptide Leu271-Ala277 inhibited thrombin-induced aggregation of platelets with an IC50 of 65 microM. The effect is specific for the activation of platelets by thrombin but not ADP or collagen. No evidence for a thrombin-kininogen complex was found, and neither HK nor its derivatives directly inhibited thrombin activity. Knowledge of the critical sequence of kininogen should allow design of compounds that can modulate thrombin activation of platelets.

11/3,AB/3  
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08517975 96141064

Rapid and efficient selection of human hematopoietic cells expressing murine heat-stable antigen as an indicator of retroviral-mediated gene transfer.

Conneally E; Bardy P; Eaves CJ; Thomas T; %%%Chappel S%%%; Shpall EJ; Humphries RK

Terry Fox Laboratory, B.C. Cancer Agency, Vancouver, Canada. Blood (UNITED STATES) Jan 15 1996, 87 (2) p456-64, ISSN 0006-4971 Journal Code: A8G

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Recombinant retroviruses offer many advantages for the genetic modification of human hematopoietic cells, although their use in clinical protocols has thus far given disappointing results. There is therefore an important need to develop new strategies that will allow effectively transduced primitive hematopoietic target populations to be both rapidly characterized and isolated free of residual nontransduced but biologically equivalent cells. To address this need, we constructed a murine stem cell virus (MSCV)-based retroviral vector containing the 228-bp coding sequence of the murine heat-stable antigen (HSA) and generated helper virus-free amphotropic MSCV-HSA producer cells by transfection of GP-env AM12 packaging cells. Light density and, in some cases, lineage marker-negative (lin-) normal human marrow or mobilized peripheral blood cells preactivated by exposure to interleukin-3 (IL-3), IL-6, and Steel factor in vitro for 48 hours were then infected by cocultivation with these MSCV-HSA producer cells for a further 48 hours in the presence of the same cytokines. Fluorescence-activated cell sorting (FACS) analysis of the cells 24 hours later showed 21% to 41% (mean, 27%) of those that were still CD34+ to have acquired the ability to express HSA. The extent of gene transfer to erythroid and granulopoietic progenitors (burst-forming unit-erythroid and colony-forming unit-granulocyte-macrophage), as assessed by the ability of these cells to form colonies of mature progeny in the presence of normally toxic concentrations of G418, averaged 11% and 12%, respectively, in 6 experiments. These values could be increased to 100% and 77%, respectively, by prior isolation of the CD34+HSA+ cell fraction and were correspondingly decreased to an average of 2% and 5%, respectively, in the CD34+HSA- cells. In addition, the extent of gene transfer to long-term culture-initiating cells (LTC-IC) was assessed by G418 resistance. The average gene transfer to LTC-IC-derived colony-forming cells in the unsorted population was < or = 7% in 4 experiments. FACS selection of the initially CD34+HSA+ cells increased this value to 86% and decreased it to 3% for the LTC-IC plated from the CD34+HSA- cells. Transfer of HSA gene expression to a phenotypically defined more primitive subpopulation of CD34+ cells, ie, those expressing little or no CD38, could also be shown by FACS analysis of infected populations 24 hours after infection. These findings underscore the potential use of retroviral vectors encoding HSA for the specific identification and non-toxic selection immediately after infection of retrovirally transduced populations of primitive human hematopoietic cells. In addition, such vectors should facilitate the subsequent tracking of their marked progeny using multiparameter flow cytometry.

11/3,AB/4

DIALOG(R)File 155:MEDLINE(R)

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08452268 96059350

Heterozygosity at the b mating-type locus attenuates %%%fusion%%% in *Ustilago maydis*.

Laity C; Giasson L; %%%Campbell R%%%; Kronstad J  
Biotechnology Laboratory, University of British Columbia, Vancouver, Canada.

Curr Genet (UNITED STATES) Apr 1995, 27 (5) p451-9, ISSN 0172-8083 Journal Code: CUG

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Mating and pathogenesis of the corn smut fungus, *Ustilago maydis*, are controlled by two unlinked mating-type loci, a and b. Yeast-like haploids that differ at both loci are compatible and fuse to establish a pathogenic dikaryon. Mating is assayed in vitro by co-inoculation on culture medium containing activated charcoal; compatible combinations have a characteristic "fuzzy" appearance caused by the growth of aerial hyphae. In general, this test has not been useful for assaying the mating ability of strains that are already mycelial (e.g., those heterozygous at b or at both mating-type loci). Using an assay for cytoduction involving transfer of a mitochondrial marker during transient cell %%%fusion%%%, and engineered strains with defined genotypes, we examined the mating abilities of strains heterozygous or hemizygous at the mating-type loci. The data (which have not been available from conventional pathogenicity or plate mating tests) show that heterozygosity at b attenuates %%%fusion%%% in haploid and diploid strains, whereas strains heterozygous at a retain the ability to fuse with a compatible haploid partner. It appears, therefore, that subsequent %%%fusion%%% events are attenuated once %%%fusion%%% has occurred to establish the *U. maydis* dikaryon.

11/3,AB/5

DIALOG(R)File 155:MEDLINE(R)

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07779954 94112125

Towards a structure of the HIV-1 envelope glycoprotein gp120: an immunochemical approach.

Moore JP; %%%Jameson BA%%%; Sattentau QJ; Willey R; Sodroski J Aaron Diamond AIDS Research Center, New York University School of Medicine, New York 10016.

Philos Trans R Soc Lond B Biol Sci (ENGLAND) Oct 29 1993, 342 (1299) p83-8, ISSN 0962-8436 Journal Code: P5Z

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The HIV-1 surface glycoprotein gp120 binds CD4 in the initial state of virus-cell %%%fusion%%%. The extensive glycosylation of gp120 has thus far precluded definition of its structure by crystallographic methods. As an initial approach to a gp120 structure, the surface topology was mapped using antibodies. First, the regions of gp120 that are accessible on the surface of the native molecule, and those that are internal but exposed after denaturation, are identified. Second, epitopes for antibodies that recognize complex surface structures comprising segments of different domains are identified. Third, we define how mutations in one domain of gp120 influence the binding of antibodies to defined epitopes on other domains. These latter approaches enable us to start to understand the inter-domain interactions that contribute to the overall structure of the gp120 molecule. Information from these studies is being used to model the structures of individual gp120 domains, and the way in which these interact in the folded protein.

11/3,AB/6

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07274543 93246012

The cloning of the human follicle stimulating hormone receptor and its expression in COS-7, CHO, and Y-1 cells.  
Kelton CA; Cheng SV; Nugent NP; Schweickhardt RL; Rosenthal JL; Overton SA; Wands GD; Kuzeja JB; Luchette CA; %%%Chappel SC%%%

Ares Advanced Technology, Inc., Randolph, MA 02368.  
Mol Cell Endocrinol (NETHERLANDS) Nov 1992, 89 (1-2) p141-51, ISSN 0303-7207 Journal Code: E69

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Follicle stimulating hormone (FSH) receptor clones were isolated from a human testis cDNA library. Characterization of the cDNA clones showed that the DNA and predicted amino acid sequences of the long open reading frame differed from a previously published human ovarian FSH receptor sequence (Minegish et al. (1991) Biochem. Biophys. Res. Commun. 175, 1125-1130) by seven nucleotides and five amino acids. A human FSH receptor splice variant was also identified and characterized. A full-length human FSH receptor cDNA was engineered for expression in COS-7, CHO, and Y-1 cells. In transient transfections of COS-7 cells and stable transfections of Y-1 cells, efficient FSH receptor mRNA accumulation and isolation of FSH-responsive cell lines occurred only when an intron was included in the 5' untranslated region of the FSH receptor transcription unit. Y-1 cells stably transfected with the FSH receptor responded to FSH treatment by rounding up and by synthesizing increased amounts of progesterone. Stably transfected CHO cell lines, which responded to FSH by synthesizing increased amounts of cAMP, were isolated irrespective of the presence of the heterologous intron. The FSH-responsive CHO and Y-1 cell lines may be suitable for the development of better in vitro FSH bioassays. These cells also constitute a convenient source of human FSH receptor protein for use in radioreceptor assays and in studies of receptor-ligand interactions.

11/3,AB/7

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07226372 93090475

Conserved structural features in the interaction between retroviral surface and transmembrane glycoproteins?

Schulz TF; %%%Jameson BA%%%; Lopalco L; Siccardi AG; Weiss RA; Moore JP Chester Beatty Laboratories, Institute of Cancer Research, London, England.

AIDS Res Hum Retroviruses (UNITED STATES) Sep 1992, 8 (9) p1571-80, ISSN 0889-2229 Journal Code: ART

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Among the retroviruses, the surface (SU) and transmembrane (TM) glycoproteins of lentiviruses are linked exclusively by noncovalent bonds. For some C-type retroviruses, however, a small proportion of the SU proteins has been shown to be linked to their TM proteins by a disulfide bond, with the remainder being noncovalently associated. A region near the carboxyl terminus of the HIV-1 SU glycoprotein has been implicated in contacting the TM glycoprotein. Computer modelling indicates that this region of divergent lentivirus and oncovirus SU glycoproteins forms a structurally conserved "pocket" which could accommodate a "knob"-like protrusion formed by an immunodominant region in the TM protein containing the CxxxxC (lentiviruses) or CxxxxxC (C- and D-type viruses) motif. An anti-idiotypic monoclonal antibody, raised against a monoclonal antibody reacting with a sequence in the "pocket" of HIV-1 gp120, was found to bind to synthetic peptides close to the CxxxxC motif. It is suggested that part of the SU-TM linkage mechanism for

the lentiviruses and oncoviruses is a 'knob and socket' structure and that the interaction between SU and TM proteins is similar in one region for lentiviruses and C-type as well as D-type viruses. The conserved knob and socket linkage may be relevant to a mechanism for viral-cell membrane %%%fusion%%% that is broadly common to all of these retroviruses.

11/3,AB/8

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06992067 91061959

Neuropsychological studies of auditory-visual %%%fusion%%% illusions. Four case studies and their implications.

%%Campbell R%%; Garwood J; Franklin S; Howard D; Landis T; Regard M University of Oxford, U.K.

Neuropsychologia (ENGLAND) 1990, 28 (8) p787-802, ISSN 0028-3932 Journal Code: NZN

Languages: ENGLISH

Document type: JOURNAL ARTICLE

A heard speech sound which is not the same as the synchronized speech sound can sometimes give rise to an illusory phonological percept. Typically, a heard /ba/ combines with a seen /ga/ to give the impression that /da/ has been heard (McGurk, H. and MacDonald, J. Nature Lond. 264, 746-748, 1976). We report the susceptibility to this illusion of four individuals with localized brain lesions affecting perceptual function. We compare their performance to that of ten control subjects and relate these findings to the efficiency of processing seen and heard speech in separate and combined modalities. The pattern of performance strongly suggests LH specialization for the phonological integration of seen and heard speech. The putative site of such integration can be effectively isolated from unilateral and from bilateral inputs and may be driven by either modality.

11/3,AB/9

DIALOG(R)File 155:MEDLINE(R)

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06011820 88300908

Identification of a novel retroviral gene unique to human immunodeficiency virus type 2 and simian immunodeficiency virus SIVMAC. Kappes JC; Morrow CD; Lee SW; %%%Jameson BA%%%; Kent SB; Hood LE; Shaw GM; Hahn BH

Department of Medicine, University of Alabama, Birmingham 35294. J Virol (UNITED STATES) Sep 1988, 62 (9) p3501-5, ISSN 0022-538X Journal Code: KCV

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Human and simian immunodeficiency-associated retroviruses are extraordinarily complex, containing at least five genes, tat, art, sor, R, and 3' orf, in addition to the structural genes gag, pol, and env. Recently, nucleotide sequence analysis of human immunodeficiency virus type 2 (HIV-2) and simian immunodeficiency virus SIVMAC revealed the existence of still another open reading frame, termed X, which is highly conserved between these two viruses but absent from HIV-1. In this report, we demonstrate for the first time that the X open reading frame represents a functional retroviral gene in both HIV-2 and SIVMAC and that it encodes a virion-associated protein of 14 and 12 kilodaltons, respectively. We also describe the production of recombinant TrpE/X %%%fusion%%% proteins in Escherichia coli and show that sera from some HIV-2-infected individuals

specifically recognize these proteins.

11/3,AB/10  
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05888398 88235916

Location and chemical synthesis of a binding site for HIV-1 on the CD4 protein.

%%Jameson BA%%; Rao PE; Kong LI; Hahn BH; Shaw GM; Hood LE; Kent SB Division of Biology, California Institute of Technology, Pasadena 91125. Science (UNITED STATES) Jun 3 1988, 240 (4857) p1335-9, ISSN 0036-8075 Journal Code: UJ7

Contract/Grant No.: A125784, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The human immunodeficiency virus type 1 (HIV-1) uses the CD4 protein as a receptor for infection of susceptible cells. A candidate structure for the HIV-1 binding site on the CD4 protein was identified by epitope mapping with a family of eight functionally distinct CD4-specific monoclonal antibodies in conjunction with a panel of large CD4-derived synthetic peptides. All of the seven epitopes that were located reside within two immunoglobulin-like disulfide loops situated between residues 1 and 168 of the CD4 protein. The CD4-specific monoclonal antibody OKT4A, a potent inhibitor of HIV-1 binding, recognized a site between residues 32 and 47 on the CD4 protein. By analogy to other members of the immunoglobulin superfamily of proteins, this particular region has been predicted to exist as a protruding loop. A synthetic analog of this loop (residues 25 to 58) showed a concentration-dependent inhibition of HIV-1-induced cell %%%fusion%%%. It is proposed that a loop extending from residues 37 to 53 of the CD4 protein is a binding site for the AIDS virus.

11/3,AB/11  
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02642988 79153202

Scoliosis and hydrocephalus in myelocoe patients. The effects of ventricular shunting.

Hall P; Lindseth R; %%%Campbell R%%%; Kalsbeck JE; Desousa A J Neurosurg (UNITED STATES) Feb 1979, 50 (2) p174-8, ISSN 0022-3085 Journal Code: JD3

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Developmental scoliosis is a common cause of increasing disability and deformity in long-term myelocoe survivors, and is believed to result from a paralytic collapsing spine. The possible etiological role of compensated hydrocephalus and hydromyelia was assessed by determining the effect of ventricular shunting on 11 myelocoe patients with developmental scoliosis. After successful shunting, one patient with a 47 degrees curve continued to deteriorate. Three cases with curves greater than 60 degrees were stabilized for short periods, but eventually required spinal %%%fusion%%%. Seven cases with curves less than 55 degrees were improved from a mean scoliosis of 29 degrees to 13 degrees during a 20-month follow-up period. Several patients had pre-existing shunts that were found to be non-functional on shuntogram. These findings suggest that the spinal complications of hydrocephalus may be more common than previously recognized in myelocoe patients and that advanced developmental scoliosis may be avoided by

early recognition and ventricular shunting. ? ds

Set	Items	Description
S1	274	E3, E6
S2	141	E3-E7
S3	3	S1 AND S2
S4	255	E3,E16
S5	84	E3,E4
S6	48	E3,E4
S7	387	S4 OR S5 OR S6
S8	3	S7 AND HYBRID
S9	11	S7 AND CHIMER?
S10	11	S9 NOT S8
S11	11	S7 AND FUSION NOT (S8 OR S9)

? logout

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\$3.48 0.116 Hrs File155

\$0.20 1 Type(s) in Format 3 (UDF)

\$5.40 27 Type(s) in Format 4 (UDF)

\$5.60 28 Types

\$9.08 Estimated cost File155

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\$113.18 Estimated total session cost 0.323 Hrs.  
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